

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/27257 A1

- (51) International Patent Classification⁷: C12N 15/00, 5/00, C12P 21/06, C07H 21/02 (74) Agent: ADLER, Benjamin, A.; McGregor & Adler, 8011 Candle Ln., Houston, TX 77071 (US).
- (21) International Application Number: PCT/US00/28558 (81) Designated States (*national*): AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 13 October 2000 (13.10.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 09/418,527 14 October 1999 (14.10.1999) US
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 01/27257 A1

(54) Title: TUMOR ANTIGEN DERIVED GENE-16 (TADG-16): A NOVEL EXTRACELLULAR SERINE PROTEASE AND USES THEREOF

(57) Abstract: The present invention provides a DNA encoding a TADG-16 protein selected from the group consisting of: (a) isolated DNA which encodes a TADG-16 protein; (b) isolated DNA which hybridizes to isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. Also provided is a vector capable of expressing the DNA of the present invention adapted for expression in a recombinant cell and regulatory elements necessary for expression of the DNA in the cell.

TUMOR ANTIGEN DERIVED GENE-16 (TADG-16): A NOVEL
5 EXTRACELLULAR SERINE PROTEASE AND USES THEREOF

10

BACKGROUND OF THE INVENTION

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Field of the Invention

The present invention relates generally to the fields of cellular biology and the diagnosis of neoplastic disease. More specifically, the present invention relates to an extracellular serine
20 protease termed Tumor Antigen Derived Gene-16 (TADG-16), which is expressed in normal ovaries and testes, as well as certain ovarian carcinomas.

Description of the Related Art

To date, ovarian cancer remains the number one killer of women with gynecologic malignant hyperplasia. Approximately 75% of women diagnosed with such cancers are already at the high-stage
5 (III and IV) of the disease at their initial diagnosis. During the past 20 years, neither diagnosis nor five year survival have greatly improved for these patients. This is substantially due to the significant number of high-stage initial detections of the disease. Therefore, the challenge remains to develop new markers to improve early diagnosis,
10 and thereby reduce the percentage of high-stage initial diagnoses.

A good tumor marker useful as an indicator of early disease is needed. Extra-cellular proteases have already been implicated in the growth, spread and metastatic progression of many cancers, thereby implying that some extracellular proteases may be
15 candidates for marker of neoplastic development. This is in part due to the ability of malignant cells not only to grow *in situ*, but to dissociate from the primary tumor and to invade new surfaces (metastasize). The ability to disengage from one tissue and re-engage the surface of another tissue is what results in the morbidity and
20 mortality associated with this disease.

In order for malignant cells to grow, spread or metastasize, they must have the capacity to invade local host tissue, dissociate or shed from the primary tumor, and for metastasis to

occur, enter and survive in the bloodstream, implant by invasion into the surface of the target organ and establish an environment conducive for new colony growth (including the induction of angiogenic and growth factors). During this progression, natural
5 tissue barriers have to be degraded, including basement membranes and connective tissue. These barriers further include collagen, laminin, proteoglycans and extracellular matrix glycoproteins, such as fibronectin.

Degradation of these natural barriers, both surrounding
10 the primary tumor and at sites of metastatic invasion, is believed to be brought about by the action of extracellular proteases. Proteases have been classified into four families: serine proteases, metallo-proteases, aspartic proteases and cysteine proteases. Many proteases have been shown to be involved in the human disease process and these enzymes
15 are targets for inhibition by new therapeutic agents.

Certain individual proteases have already been shown to be induced and overexpressed in a diverse group of cancers, and as such, are potential candidates for markers useful for early diagnosis and possibly therapeutic intervention. Examples of proteases,
20 encompassing members of the metallo-proteases, serine proteases, and cysteine proteases, are listed below.

TABLE 1Protease Expression in Various Cancers

		<u>Gastric</u>	<u>Brain</u>	<u>Breast</u>	<u>Ovarian</u>
5	Serine Proteases	uPA PAI-1	uPA PAI-1	NES-1 uPA	NES-1 PAI-2
10	Cysteine Proteases	Cathepsin Cathepsin	B Cathepsin L	L Cathepsin Cathepsin	B Cathepsin L Cathepsin
	Metallo- proteases	Matrilysin* Collagenase* Stromelysin-1*	Matrilysin Stromelysin Gelatinase B	Stromelysin-3 MMP-8 MMP-9	MMP-2
15	<u>Gelatinase A</u>				
	uPA, Urokinase-type	plasminogen	activator;	tPA, Tissue-type	
	plasminogen activator; PAI-I, Plasminogen	activator	0 inhibitors; PAI-2,		
	Plasminogen activator inhibitors; NES-1, Normal	epithelial cell-			
	specific-1; MMP, Matrix P metallo-protease.				
20	*Overexpressed in gastrointestinal ulcers.				

Significantly, there is a good body of evidence supporting the down regulation or inhibition of individual proteases and a subsequent reduction in invasive capacity or malignancy. In work by Clark *et al.*, (*Peptides*, 14, 1021-8 (1993)) inhibition of *in vitro* growth of human small cell lung cancer was demonstrated using a general serine protease inhibitor. More recently, Torres-Rosedo *et al.*, (*Proc. Natl. Acad. Sci. USA*, 90, 7181-7185 (1993)) demonstrated an

inhibition of hepatoma tumor cell growth using specific antisense inhibitors for the serine protease hepsin gene. Metastatic potential has also been shown to be reduced using a synthetic inhibitor (batimastat) of metallo-protease in a mouse model with melanoma cells. Powell *et al.* (*Cancer Research*, 53, 417-422 (1993)) presented evidence to confirm that the expression of extracellular proteases in relatively non-invasive tumor cells enhances their malignant progression using a tumor-genic, but non-metastatic, prostate cell line. Specifically, Powell *et al.* demonstrated enhanced metastasis after introducing and expressing the PUMP-1 metallo-protease gene. There is also a body of data to support the notion that expression of cell surface proteases on relatively non-metastatic cell types increases the invasive potential of such cells.

Extracellular proteases have been directly associated with tumor growth, shedding of tumor cells and invasion of target organs by tumors. Individual classes of proteases are involved in, but not limited to, (a) digestion of stroma surrounding the initial tumor area; (b) digestion of the cellular adhesion molecules to allow dissociation of tumor cells; and (c) invasion of the basement membrane for metastatic growth and the activation of both tumor growth factors and angiogenic factors.

Interfering in the intracellular signal transduction pathways provides mechanisms for numerous therapeutic

applications. While several proteins have been identified that interfere with various signal transduction mechanisms, novel proteins involved in signal transduction pathways are important to provide alternatives for therapy and drug development.

5 The prior art is deficient in that the prior art lacks the nucleotide and amino acid sequences corresponding to tumor antigen-derived gene 16 (TADG-16). The prior art further lacks effective means of screening to identify proteases, specifically TADG-16, expressed in normal ovaries and testes and certain ovarian
10 carcinomas. The present invention fulfills this longstanding need and desire in the art.

SUMMARY OF THE INVENTION

15 This invention describes a new serine protease enzyme. The TADG-16 enzyme contains the characteristic features of a serine protease, including the conserved catalytic triad (His-Asp-Ser) and a secretion signal sequence. The TADG-16 transcript is present in carcinomas and normal ovarian tissues as well as in normal testes.
20 Because TADG-16 is secreted and has a potential for extracellular activation, TADG-16 may have a role in normal or aberrant physiological activity of ovary or testes.

In one embodiment of the present invention, there is provided a DNA encoding a tumor antigen-derived gene (TADG-16) protein, selected from the following: (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes
5 under high stringency conditions to the isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. The embodiment further includes a vector comprising the
10 TADG-16 DNA and regulatory elements necessary for expression of the DNA in a cell. Additionally embodied is a vector in which the TADG-16 DNA is positioned in reverse orientation relative to the regulatory elements such that TADG-16 antisense mRNA is produced.

In another embodiment of the present invention, there is
15 provided an isolated and purified TADG-16 protein coded for by DNA selected from the following: (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the
20 isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein.

In yet another embodiment of the present invention, there is provided a method for detecting TADG-16 mRNA in a sample, comprising the steps of (a) contacting a sample with a probe which is specific for TADG-16; and (b) detecting binding of the probe to TADG-
5 16 mRNA in the sample. In still yet another embodiment of the present invention, there is provided a kit for detecting TADG-16 mRNA, comprising an oligonucleotide probe specific for TADG-16. A label for detection is further embodied in the kit.

The present invention additionally embodies a method of
10 detecting TADG-16 protein in a sample, comprising the steps of (a) contacting a sample with an antibody which is specific for TADG-16 or a fragment thereof; and (b) detecting binding of the antibody to TADG-16 protein in the sample. Similarly, the present invention also embodies a kit for detecting TADG-16 protein, comprising an antibody
15 specific for TADG-16 protein or a fragment thereof. Means for detection of the antibody is further embodied in the kit.

In another embodiment, the present invention provides an antibody specific for the TADG-16 protein or a fragment thereof.

In yet another embodiment, the present invention provides
20 a method of screening for compounds that inhibit TADG-16, comprising the steps of (a) contacting a sample comprising TADG-16 protein with a compound; and (b) assaying for TADG-16 protease activity. Typically, a decrease in the TADG-16 protease activity in the

presence of the compound relative to TADG-16 protease activity in the absence of the compound is indicative of a compound that inhibits TADG-16.

In still yet another embodiment of the present invention,
5 there is provided a method of inhibiting expression of TADG-16 in a cell, comprising the step of (a) introducing a vector into a cell, whereupon expression of the vector produces TADG-16 antisense mRNA in the cell which hybridizes to endogenous TADG-16 mRNA, thereby inhibiting expression of TADG-16 in the cell.

10 Further embodied by the present invention, there is provided a method of inhibiting a TADG-16 protein in a cell, comprising the step of (a) introducing an antibody specific for a TADG-16 protein or a fragment thereof into a cell, whereupon binding of the antibody to the TADG-16 protein inhibits the TADG-16 protein.

15 In another embodiment of the present invention, there is provided a method of targeted therapy to an individual, comprising the step of (a) administering a compound containing a targeting moiety and a therapeutic moiety to an individual, wherein the targeting moiety is specific for TADG-16.

20 In another embodiment of the present invention, there is provided a method of diagnosing cancer in an individual, comprising the steps of (a) obtaining a biological sample from an individual; and (b) detecting TADG-16 in the sample. Typically, the presence of

TADG-16 in the sample is indicative of the presence of carcinoma in the individual and the absence of TADG-16 in the sample is indicative of the absence of carcinoma in the individual.

In another embodiment of the present invention, there is provided a method of vaccinating an individual against TADG-16, comprising the steps of (a) inoculating an individual with a TADG-16 protein or fragment thereof that lacks TADG-16 protease activity. It is intended that inoculation with the TADG-16 protein or fragment thereof elicits an immune response in the individual, thereby vaccinating the individual against TADG-16.

In another embodiment of the present invention, there is provided an immunogenic composition, comprising an immunogenic fragment of TADG-16 and an appropriate adjuvant.

Other and further aspects, features, and advantages of the present invention will be apparent from the following description of the presently preferred embodiments of the invention given for the purpose of disclosure.

20

BRIEF DESCRIPTION OF THE DRAWINGS

So that the matter in which the above-recited features, advantages and objects of the invention, as well as others which will

become clear, are attained and can be understood in detail, more particular descriptions of the invention briefly summarized above may be had by reference to certain embodiments thereof which are illustrated in the appended drawings. These drawings form a part of
5 the specification. It is to be noted, however, that the appended drawings illustrate preferred embodiments of the invention and therefore are not to be considered limiting in their scope.

Figure 1 shows an alignment of a portion of the TADG-16 protein sequence (SEQ ID No. 7) with other known proteases (Prom,
10 Protease M (SEQ ID No. 3); Try1, Trypsinogen 1 (SEQ ID No. 4); SCCE, Stratum corneum chymotryptic like enzyme (SEQ ID No. 5); and Heps, Hepsin (SEQ ID No. 6)).

Figure 2 shows Northern blot analysis of multiple human tissues using the radioactively labeled catalytic domain as a probe.
15 The 1.4 Kb TADG-16 transcript is present in normal human testes and in certain ovarian tumors, but is not detectable at significant levels in other tissues examined. Hybridization of mRNA to β -tubulin is shown as an internal control.

Figure 3A shows the nucleotide and predicted amino acid
20 sequence of the original subclone from the WISH cDNA containing the TADG-16 catalytic domain. **Figure 3B** shows a sequence identified from the EST database (Accession #AA620757) with homology to the TADG-16 catalytic domain (encoding bases 614 to 1129) and

including the 3'-untranslated region and poly (A) tail of the TADG-16 transcript.

Figure 4 shows the nucleotide sequence of the TADG-16 cDNA and the predicted amino acid sequence. The cDNA
5 corresponding to TADG-16 contains a Kozak's consensus sequence (boxed nucleotides) for the initiation of translation from which a putative protein of 314 amino acids is encoded. The protein contains a secretion signal sequence (italicized) and the conserved amino acids of the catalytic triad of the serine protease family (circled) in the
10 appropriate context (underlined residues). The cDNA also contains a polyadenylation sequence in the 3' untranslated region (underlined nucleotides).

Figure 5 shows TADG-16 (and β -tubulin) expression in normal and carcinoma cell lines.

15 **Figure 6** shows TADG-16 expression in normal (N), benign (B), low malignant potential (LMP) tumors and carcinomas (C). **Figure 6A** shows quantitative PCR of TADG-16 (250 bp) and internal control, β -tubulin (470 bp). *Lanes 1-3*, normal ovary (cases 5-7, respectively); *Lanes 4-5*, benign mucinous adenoma tumor (cases 8 & 11, respectively); *Lane 6*, serous LMP tumor (case 14); *Lanes 7-8*, clear
20 cell carcinoma (cases 20 & 21, respectively); *Lanes 9-11*, serous adenocarcinoma (cases 22, 29 and 32, respectively); *Lane 12*, endometrioid adenocarcinoma (case 35). **Figure 6B** shows a graph

of expression of TADG-16 in normal ovaries and ovarian benign, LMP and carcinoma tumors.

5 DETAILED DESCRIPTION OF THE INVENTION

This invention describes a new serine protease enzyme complementary to the series of proteases already identified and characterized in ovarian carcinoma. The TADG-16 enzyme contains
10 the characteristic features of all serine proteases, including the conserved catalytic triad of His-Asp-Ser and a signal secretion sequence. The transcript for this enzyme is present in carcinomas and normal ovarian tissues as well as in normal testes. Because TADG-16 is secreted and has a potential for extracellular activation, TADG-
15 16 may have a role in normal or aberrant physiological activity (*i.e.*, normal or carcinomatous growth) of ovary or testes. Furthermore, because of the presence of TADG-16 mRNA in normal testes, there is a potential role for TADG-16 in normal testicular function (*e.g.*, sterility).

20 The TADG-16 cDNA is 1129 base pairs long (SEQ ID No. 1) and encodes a 314 amino acid protein (SEQ ID No. 2).

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and

recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, Maniatis, Fritsch & Sambrook, "Molecular Cloning: A Laboratory Manual (1982); "DNA Cloning: A Practical Approach," Volumes I and II (D.N. Glover ed. 5 1985); "Oligonucleotide Synthesis" (M.J. Gait ed. 1984); "Nucleic Acid Hybridization" [B.D. Hames & S.J. Higgins eds. (1985)]; "Transcription and Translation" [B.D. Hames & S.J. Higgins eds. (1984)]; "Animal Cell Culture" [R.I. Freshney, ed. (1986)]; "Immobilized Cells And Enzymes" [IRL Press, (1986)]; B. Perbal, "A Practical Guide To Molecular Cloning" 10 (1984).

Therefore, if appearing herein, the following terms shall have the definitions set out below.

As used herein, the term "cDNA" shall refer to the DNA copy of the mRNA transcript of a gene.

15 As used herein, the term "derived amino acid sequence" shall mean the amino acid sequence determined by reading the triplet sequence of nucleotide bases in the cDNA.

As used herein the term "screening a library" shall refer to the process of using a labeled probe to check whether, under the 20 appropriate conditions, there is a sequence complementary to the probe present in a particular DNA library. In addition, "screening a library" could be performed by PCR.

As used herein, the term "PCR" refers to the Polymerase Chain Reaction that is the subject of U.S. Patent Nos. 4,683,195 and 4,683,202 to Mullis, as well as other improvements to the process/technique of PCR now known in the art.

5 The amino acid described herein are preferred to be in the "L" isomeric form. However, residues in the "D" isomeric form can be substituted for any L-amino acid residue, as long as the desired functional property of immunoglobulin-binding is retained by the polypeptide. NH₂ refers to the free amino group present at the amino
10 terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxy terminus of a polypeptide. In keeping with standard polypeptide nomenclature, *J Biol. Chem.*, 243:3552-59 (1969), abbreviations for amino acid residues are shown in Table 2.

15 **TABLE 2**

<u>Symbol</u>		<u>Amino acid</u>
<u>1 Letter</u>	<u>3 Letter</u>	
A	Ala	Alanine
C	Cys	Cysteine
20 D	Asp	Aspartic acid
E	Glu	Glutamic acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
25 I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine

	P	Pro	Proline
	Q	Gln	Glutamine
	R	Arg	Arginine
	S	Ser	Serine
5	T	Thr	Threonine
	V	Val	Valine
	W	Trp	Tryptophan
	Y	Tyr	Tyrosine

10 It should be noted that all amino-acid residue sequences are represented herein by formulae whose left and right orientation is in the conventional direction of amino-terminus to carboxy-terminus. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further
15 sequence of one or more amino-acid residues. The above table is presented to correlate the three-letter and one-letter notations which may appear alternately herein.

 A "replicon" is any genetic element (*e.g.*, plasmid, chromosome, virus) that functions as an autonomous unit of DNA
20 replication *in vivo*; *i.e.*, capable of replication under its own control.

 A "vector" is a replicon, such as plasmid, phage or cosmid, to which another DNA segment may be attached so as to bring about the replication of the attached segment.

 A "DNA molecule" refers to the polymeric form of
25 deoxyribonucleotides (adenine, guanine, thymine, or cytosine) in its either single stranded form, or a double-stranded helix. This term refers only to the primary and secondary structure of the molecule,

and does not limit it to any particular tertiary forms. Thus, this term includes double-stranded DNA found, *inter alia*, in linear DNA molecules (*e.g.*, restriction fragments), viruses, plasmids, and chromosomes. The structure is discussed herein according to the
5 normal convention of giving only the 5' to 3' sequence of the nontranscribed strand of DNA (*i.e.*, the strand having a sequence homologous to the mRNA).

An "origin of replication" refers to those DNA sequences that participate in DNA synthesis.

10 A DNA "coding sequence" is a double-stranded DNA sequence which is transcribed and translated into a polypeptide *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5' (amino) terminus and a translation stop codon
15 at the 3' (carboxyl) terminus. A coding sequence can include, but is not limited to, prokaryotic sequences, cDNA from eukaryotic mRNA, genomic DNA sequences from eukaryotic (*e.g.*, mammalian) DNA, and even synthetic DNA sequences. A polyadenylation signal and transcription termination sequence will usually be located 3' to the
20 coding sequence.

Transcriptional and translational control sequences are DNA regulatory sequences, such as promoters, enhancers,

polyadenylation signals, terminators, and the like, that provide for the expression of a coding sequence in a host cell.

A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of defining the present invention, the promoter sequence is bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site, as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eukaryotic promoters often, but not always, contain "TATA" boxes and "CAT" boxes. Prokaryotic promoters contain Shine-Dalgarno sequences in addition to the -10 and -35 consensus sequences.

An "expression control sequence" is a DNA sequence that controls and regulates the transcription and translation of another DNA sequence. A coding sequence is "under the control" of transcriptional and translational control sequences in a cell when RNA polymerase transcribes the coding sequence into mRNA, which is then translated into the protein encoded by the coding sequence.

A "signal sequence" can be included near the coding sequence. This sequence encodes a signal peptide, N-terminal to the polypeptide, that communicates to the host cell to direct the polypeptide to the cell surface or secrete the polypeptide into the media, and this signal peptide is clipped off by the host cell before the protein leaves the cell. Signal sequences can be found associated with a variety of proteins native to prokaryotes and eukaryotes.

The term "oligonucleotide", as used herein in referring to the probe of the present invention, is defined as a molecule comprised of two or more ribonucleotides, preferably more than three. Its exact size will depend upon many factors which, in turn, depend upon the ultimate function and use of the oligonucleotide.

The term "primer" as used herein refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product, which is complementary to a nucleic acid strand, is induced, *i.e.*, in the presence of nucleotides and an inducing agent such as a DNA polymerase and at a suitable temperature and pH. The primer may be either single-stranded or double-stranded and must be sufficiently long to prime the synthesis of the desired extension product in the presence of the inducing agent. The exact length of the primer will

depend upon many factors, including temperature, source of primer and use the method. For example, for diagnostic applications, depending on the complexity of the target sequence, the oligonucleotide primer typically contains 15-25 or more nucleotides, 5 although it may contain fewer nucleotides.

The primers herein are selected to be "substantially" complementary to different strands of a particular target DNA sequence. This means that the primers must be sufficiently complementary to hybridize with their respective strands. Therefore, 10 the primer sequence need not reflect the exact sequence of the template. For example, a non-complementary nucleotide fragment may be attached to the 5' end of the primer, with the remainder of the primer sequence being complementary to the strand. Alternatively, non-complementary bases or longer sequences can be interspersed 15 into the primer, provided that the primer sequence has sufficient complementary with the sequence or hybridize therewith and thereby form the template for the synthesis of the extension product.

As used herein, the terms "restriction endonucleases" and "restriction enzymes" refer to enzymes, each of which cut double- 20 stranded DNA at or near a specific nucleotide sequence.

A cell has been "transformed" by exogenous or heterologous DNA when such DNA has been introduced inside the cell. The transforming DNA may or may not be integrated (covalently

linked) into the genome of the cell. In prokaryotes, yeast, and mammalian cells for example, the transforming DNA may be maintained on an episomal element such as a plasmid. With respect to eukaryotic cells, a stably transformed cell is one in which the transforming DNA has become integrated into a chromosome so that it is inherited by daughter cells through chromosome replication. This stability is demonstrated by the ability of the eukaryotic cell to establish cell lines or clones comprised of a population of daughter cells containing the transforming DNA. A "clone" is a population of cells derived from a single cell or ancestor by mitosis. A "cell line" is a clone of a primary cell that is capable of stable growth *in vitro* for many generations.

Two DNA sequences are "substantially homologous" when at least about 75% (preferably at least about 80%, and most preferably at least about 90% or 95%) of the nucleotides match over the defined length of the DNA sequences. Sequences that are substantially homologous can be identified by comparing the sequences using standard software available in sequence data banks, or in a Southern hybridization experiment under, for example, stringent conditions as defined for that particular system. Defining appropriate hybridization conditions is within the skill of the art. See, *e.g.*, Maniatis et al., *supra*; DNA Cloning, Vols. I & II, *supra*; Nucleic Acid Hybridization, *supra*.

A "heterologous" region of the DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. In another example, coding sequence is a construct where the coding sequence itself is not found in nature (*e.g.*, a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

The labels most commonly employed for these studies are radioactive elements, enzymes, chemicals which fluoresce when exposed to ultraviolet light, and others. A number of fluorescent materials are known and can be utilized as labels. These include, for example, fluorescein, rhodamine, auramine, Texas Red, AMCA blue and Lucifer Yellow. A particular detecting material is anti-rabbit antibody prepared in goats and conjugated with fluorescein through an isothiocyanate.

Proteins can also be labeled with a radioactive element or with an enzyme. The radioactive label can be detected by any of the currently available counting procedures. The preferred isotope may

be selected from ^3H , ^{14}C , ^{32}P , ^{35}S , ^{36}Cl , ^{51}Cr , ^{57}Co , ^{58}Co , ^{59}Fe , ^{90}Y , ^{125}I , ^{131}I , and ^{186}Re .

Enzyme labels are likewise useful, and can be detected by any of the presently utilized colorimetric, spectrophotometric, 5 fluorospectrophotometric, amperometric or gasometric techniques. The enzyme is conjugated to the selected particle by reaction with bridging molecules such as carbodiimides, diisocyanates, glutaraldehyde and the like. Many enzymes which can be used in these procedures are known and can be utilized. The preferred are 10 peroxidase, β -glucuronidase, β -D-glucosidase, β -D-galactosidase, urease, glucose oxidase plus peroxidase and alkaline phosphatase. U.S. Patent Nos. 3,654,090, 3,850,752, and 4,016,043 are referred to by way of example for their disclosure of alternate labeling material and methods.

15 A particular assay system developed and utilized in the art is known as a receptor assay. In a receptor assay, the material to be assayed is appropriately labeled and then certain cellular test colonies are inoculated with a quantity of both the label after which binding studies are conducted to determine the extent to which the labeled 20 material binds to the cell receptors. In this way, differences in affinity between materials can be ascertained.

An assay useful in the art is known as a "cis/trans" assay. Briefly, this assay employs two genetic constructs, one of which is

typically a plasmid that continually expresses a particular receptor of interest when transfected into an appropriate cell line, and the second of which is a plasmid that expresses a reporter such as luciferase, under the control of a receptor/ligand complex. Thus, for example, if
5 it is desired to evaluate a compound as a ligand for a particular receptor, one of the plasmids would be a construct that results in expression of the receptor in the chosen cell line, while the second plasmid would possess a promoter linked to the luciferase gene in which the response element to the particular receptor is inserted. If
10 the compound under test is an agonist for the receptor, the ligand will complex with the receptor, and the resulting complex will bind the response element and initiate transcription of the luciferase gene. The resulting chemiluminescence is then measured photometrically, and dose response curves are obtained and compared to those of
15 known ligands. The foregoing protocol is described in detail in U.S. Patent No. 4,981,784.

As used herein, the term "host" is meant to include not only prokaryotes but also eukaryotes such as yeast, plant and animal cells. A recombinant DNA molecule or gene which encodes a human
20 TADG-16 protein of the present invention can be used to transform a host using any of the techniques commonly known to those of ordinary skill in the art. Especially preferred is the use of a vector containing coding sequences for the gene which encodes a human

TADG-16 protein of the present invention for purposes of prokaryote transformation. Prokaryotic hosts may include *E. coli*, *S. typhimurium*, *Serratia marcescens* and *Bacillus subtilis*. Eukaryotic hosts include yeasts such as *Pichia pastoris*, mammalian cells and
5 insect cells.

In general, expression vectors containing promoter sequences which facilitate the efficient transcription of the inserted DNA fragment are used in connection with the host. The expression vector typically contains an origin of replication, promoter(s),
10 terminator(s), as well as specific genes which are capable of providing phenotypic selection in transformed cells. The transformed hosts can be fermented and cultured according to means known in the art to achieve optimal cell growth.

The invention includes a substantially pure DNA encoding
15 a TADG-16 protein, a strand of which DNA will hybridize at high stringency to a probe containing a sequence of at least 15 consecutive nucleotides of SEQ ID No. 1. The protein encoded by the DNA of this invention may share at least 80% sequence identity (preferably 85%, more preferably 90%, and most preferably 95%)
20 with the amino acids shown in SEQ ID No. 2. More preferably, the DNA includes the coding sequence of the nucleotides shown in SEQ ID No. 1, or a degenerate variant of such a sequence.

The probe to which the DNA of the invention hybridizes preferably consists of a sequence of at least 20 consecutive nucleotides, more preferably 40 nucleotides, even more preferably 50 nucleotides, and most preferably 100 nucleotides or more (up to 5 100%) of the coding sequence of the nucleotides shown in SEQ ID No. 1 or the complement thereof. Such a probe is useful for detecting expression of TADG-16 in a cell by a method including the steps of (a) contacting mRNA obtained from the cell with the labeled hybridization probe; and (b) detecting hybridization of the probe 10 with the mRNA.

This invention also includes a substantially pure DNA containing a sequence of at least 15 consecutive nucleotides (preferably 20, more preferably 30, even more preferably 50, and most preferably all) of the region from nucleotides 1 to 3147 of the 15 nucleotides shown in SEQ ID No. 1.

By "high stringency" is meant DNA hybridization and wash conditions characterized by high temperature and low salt concentration, *e.g.*, wash conditions of 65°C at a salt concentration of approximately 0.1 x SSC, or the functional equivalent thereof. For 20 example, high stringency conditions may include hybridization at about 42°C in the presence of about 50% formamide; a first wash at about 65°C with about 2 x SSC containing 1% SDS; followed by a second wash at about 65°C with about 0.1 x SSC.

By "substantially pure DNA" is meant DNA that is not part of a milieu in which the DNA naturally occurs, by virtue of separation (partial or total purification) of some or all of the molecules of that milieu, or by virtue of alteration of sequences that flank the claimed
5 DNA. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (*e.g.*, a cDNA or a genomic or cDNA fragment produced by polymerase chain reaction
10 (PCR) or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence, *e.g.*, a fusion protein. Also included is a recombinant DNA which includes a portion of the nucleotides shown in SEQ ID No. 1 which encodes an
15 alternative splice variant of TADG-16.

The DNA may have at least about 70% sequence identity to the coding sequence of the nucleotides shown in SEQ ID No. 1, preferably at least 75% (*e.g.*, at least 80%); and most preferably at least 90%. The identity between two sequences is a direct function of
20 the number of matching or identical positions. When a subunit position in both of the two sequences is occupied by the same monomeric subunit, *e.g.*, if a given position is occupied by an adenine in each of two DNA molecules, then they are identical at that

position. For example, if 7 positions in a sequence 10 nucleotides in length are identical to the corresponding positions in a second 10-nucleotide sequence, then the two sequences have 70% sequence identity. The length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75 nucleotides, and most preferably 100 nucleotides. Sequence identity is typically measured using sequence analysis software (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705).

The present invention is directed towards a vector comprising a DNA sequence which encodes a TADG-16 protein, wherein the vector is capable of replication in a host cell, wherein the vector comprises, in operable linkage: a) an origin of replication; b) a promoter; and c) a DNA sequence coding for the TADG-16 protein. Preferably, the vector of the present invention contains a portion of the DNA sequence shown in SEQ ID No. 1.

A "vector" may be defined as a replicable nucleic acid construct, *e.g.*, a plasmid or viral nucleic acid. Vectors may be used to amplify and/or express nucleic acid encoding TADG-16 protein. An expression vector is a replicable construct in which a nucleic acid sequence encoding a polypeptide is operably linked to suitable control sequences capable of effecting expression of the polypeptide

in a cell. The need for such control sequences will vary depending upon the cell selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter and/or enhancer, suitable mRNA ribosomal binding sites, and
5 sequences which control the termination of transcription and translation.

Methods which are well known to those skilled in the art can be used to construct expression vectors containing appropriate transcriptional and translational control signals. See for example, the
10 techniques described in Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual* (2nd Ed.), Cold Spring Harbor Press, N.Y. A gene and its transcription control sequences are defined as being "operably linked" if the transcription control sequences effectively control the transcription of the gene. Vectors of the invention
15 include, but are not limited to, plasmid vectors and viral vectors. Preferred viral vectors of the invention are those derived from retroviruses, adenovirus, adeno-associated virus, SV40 virus, or herpes viruses.

By a "substantially pure protein" is meant a protein which
20 has been separated from at least some of those components which naturally accompany it. Typically, the protein is substantially pure when it is at least 60%, by weight, free from the proteins and other naturally-occurring organic molecules with which it is naturally

associated *in vivo*. Preferably, the purity of the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight. A substantially pure TADG-16 protein may be obtained, for example, by extraction from a natural source; by expression of a recombinant nucleic acid encoding an TADG-16 polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, *e.g.*, column chromatography such as immunoaffinity chromatography using an antibody specific for TADG-16, polyacrylamide gel electrophoresis, or HPLC analysis. A protein is substantially free of naturally associated components when it is separated from at least some of those contaminants which accompany it in its natural state. Thus, a protein which is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates will be, by definition, substantially free from its naturally associated components. Accordingly, substantially pure proteins include eukaryotic proteins synthesized in *E. coli*, other prokaryotes, or any other organism in which they do not naturally occur.

In addition to substantially full-length proteins, the invention also includes fragments (*e.g.*, antigenic fragments) of the TADG-16 protein (SEQ ID No. 2). As used herein, "fragment," as applied to a polypeptide, will ordinarily be at least 10 residues, more typically at least 20 residues, and preferably at least 30 (*e.g.*,

50) residues in length, but less than the entire, intact sequence. Fragments of the TADG-16 protein can be generated by methods known to those skilled in the art, *e.g.*, by enzymatic digestion of naturally occurring or recombinant TADG-16 protein, by
5 recombinant DNA techniques using an expression vector that encodes a defined fragment of TADG-16, or by chemical synthesis. The ability of a candidate fragment to exhibit a characteristic of TADG-16 (*e.g.*, binding to an antibody specific for TADG-16) can be assessed by methods described herein. Purified TADG-16 or antigenic fragments
10 of TADG-16 can be used to generate new antibodies or to test existing antibodies (*e.g.*, as positive controls in a diagnostic assay) by employing standard protocols known to those skilled in the art.

Included in this invention are polyclonal antisera generated by using TADG-16 or a fragment of TADG-16 as the
15 immunogen in, *e.g.*, rabbits. Standard protocols for monoclonal and polyclonal antibody production known to those skilled in this art are employed. The monoclonal antibodies generated by this procedure can be screened for the ability to identify recombinant TADG-16 cDNA clones, and to distinguish them from known cDNA clones.

20 Further included in this invention are TADG-16 proteins which are encoded at least in part by portions of SEQ ID No. 2, *e.g.*, products of alternative mRNA splicing or alternative protein processing events, or in which a section of TADG-16 sequence has

been deleted. The fragment, or the intact TADG-16 polypeptide, may be covalently linked to another polypeptide, *e.g.*, which acts as a label, a ligand or a means to increase antigenicity.

The invention also includes a polyclonal or monoclonal
5 antibody which specifically binds to TADG-16. The invention encompasses not only an intact monoclonal antibody, but also an immunologically-active antibody fragment, *e.g.*, a Fab or (Fab)₂ fragment; an engineered single chain Fv molecule; or a chimeric molecule, *e.g.*, an antibody which contains the binding specificity of
10 one antibody, *e.g.*, of murine origin, and the remaining portions of another antibody, *e.g.*, of human origin.

In one embodiment, the antibody, or a fragment thereof, may be linked to a toxin or to a detectable label, *e.g.*, a radioactive label, non-radioactive isotopic label, fluorescent label,
15 chemiluminescent label, paramagnetic label, enzyme label, or colorimetric label. Examples of suitable toxins include diphtheria toxin, *Pseudomonas* exotoxin A, ricin, and cholera toxin. Examples of suitable enzyme labels include malate hydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, alcohol dehydrogenase, alpha-
20 glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, acetylcholinesterase, etc.

Examples of suitable radioisotopic labels include ^3H , ^{125}I , ^{131}I , ^{32}P , ^{35}S , ^{14}C , etc.

Paramagnetic isotopes for purposes of *in vivo* diagnosis can also be used according to the methods of this invention. There are numerous examples of elements that are useful in magnetic resonance imaging. For discussions on *in vivo* nuclear magnetic resonance imaging, see, for example, Schaefer et al., (1989) *JACC* 14, 472-480; Shreve et al., (1986) *Magn. Reson. Med.* 3, 336-340; Wolf, G. L., (1984) *Physiol. Chem. Phys. Med. NMR* 16, 93-95; Wesbey et al., (1984) *Physiol. Chem. Phys. Med. NMR* 16, 145-155; Runge et al., (1984) *Invest. Radiol.* 19, 408-415. Examples of suitable fluorescent labels include a fluorescein label, an isothiocyalate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, an ophthaldehyde label, a fluorescamine label, etc. Examples of chemiluminescent labels include a luminal label, an isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, an aequorin label, etc.

Those of ordinary skill in the art will know of other suitable labels which may be employed in accordance with the present invention. The binding of these labels to antibodies or fragments thereof can be accomplished using standard techniques commonly known to those of ordinary skill in the art. Typical

techniques are described by Kennedy et al., (1976) *Clin. Chim. Acta* 70, 1-31; and Schurs et al., (1977) *Clin. Chim. Acta* 81, 1-40. Coupling techniques mentioned in the latter are the glutaraldehyde method, the periodate method, the dimaleimide method, the m-
5 maleimidobenzyl-N-hydroxy-succinimide ester method. All of these methods are incorporated by reference herein.

Also within the invention is a method of detecting TADG-16 protein in a biological sample, which includes the steps of contacting the sample with the labeled antibody, *e.g.*, radioactively
10 tagged antibody specific for TADG-16, and determining whether the antibody binds to a component of the sample.

As described herein, the invention provides a number of diagnostic advantages and uses. For example, the TADG-16 protein is useful in diagnosing cancer in different tissues since this protein is
15 highly overexpressed in tumor cells. Antibodies (or antigen-binding fragments thereof) which bind to an epitope specific for TADG-16, are useful in a method of detecting TADG-16 protein in a biological sample for diagnosis of cancerous or neoplastic transformation. This method includes the steps of obtaining a biological sample (*e.g.*,
20 cells, blood, plasma, tissue, etc.) from a patient suspected of having cancer, contacting the sample with a labeled antibody (*e.g.*, radioactively tagged antibody) specific for TADG-16, and detecting the TADG-16 protein using standard immunoassay techniques such as

an ELISA. Antibody binding to the biological sample indicates that the sample contains a component which specifically binds to an epitope within TADG-16.

Likewise, a standard Northern blot assay can be used to
5 ascertain the relative amounts of TADG-16 mRNA in a cell or tissue obtained from a patient suspected of having cancer, in accordance with conventional Northern hybridization techniques known to those of ordinary skill in the art. This Northern assay uses a hybridization probe, *e.g.*, radiolabelled TADG-16 cDNA, either containing the full-
10 length, single stranded DNA having a sequence complementary to SEQ ID No. 1, or a fragment of that DNA sequence at least 20 (preferably at least 30, more preferably at least 50, and most preferably at least 100) consecutive nucleotides in length. The DNA hybridization probe can be labeled by any of the many different methods known to those
15 skilled in this art.

Antibodies to the TADG-16 protein can be used in an immunoassay to detect increased levels of TADG-16 protein expression in tissues suspected of neoplastic transformation. These same uses can be achieved with Northern blot assays and analyses.

20 The TADG-16 cDNA is 1129 base pairs long (SEQ ID No. 1) encoding for a 314 amino acid protein (SEQ ID No. 2). The availability of the TADG-16 gene provides numerous utilities. For example, the TADG-16 gene can be used as a diagnostic or therapeutic target in

ovarian and other carcinomas, including breast, prostate, lung and colon.

The present invention is directed to DNA encoding a tumor antigen-derived gene (TADG-16) protein, selected from (a) an isolated
5 DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to the isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon
10 encodes a TADG-16 protein. It is preferred that the DNA has the sequence shown in SEQ ID No. 1 and the TADG-16 protein has the amino acid sequence shown in SEQ ID No. 2.

The present invention is directed toward a vector comprising the TADG-16 DNA and regulatory elements necessary for
15 expression of the DNA in a cell, or a vector in which the TADG-16 DNA is positioned in reverse orientation relative to the regulatory elements such that TADG-16 antisense mRNA is produced. An antisense molecule corresponding to TADG-16 mRNA is shown in SEQ ID No. 16. The invention is also directed toward host cells transfected with either
20 of the above-described vector(s). Representative host cells are bacterial cells, mammalian cells, plant cells and insect cells. Preferably, the bacterial cell is *E. coli*.

The present invention is directed toward an isolated and purified TADG-16 protein coded for by DNA selected from the following: (a) an isolated DNA which encodes a TADG-16 protein; (b) an isolated DNA which hybridizes under high stringency conditions to
5 isolated DNA of (a) above and which encodes a TADG-16 protein; and (c) an isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein. Preferably, the protein has the amino acid sequence shown in SEQ ID No. 2.

10 The present invention is directed toward a method for detecting TADG-16 mRNA in a sample, comprising the steps of (a) contacting a sample with a probe which is specific for TADG-16; and (b) detecting binding of the probe to TADG-16 mRNA in the sample. The present invention is also directed toward a method of detecting
15 TADG-16 protein in a sample, comprising the steps of (a) contacting a sample with an antibody which is specific for TADG-16 or a fragment thereof; and (b) detecting binding of the antibody to TADG-16 protein in the sample. Generally, the sample is a biological sample; preferably, the biological sample is from an individual; and typically,
20 the individual is suspected of having cancer.

The present invention is directed toward a kit for detecting TADG-16 mRNA, comprising an oligonucleotide probe, wherein the probe is specific for TADG-16. The kit may further comprise a label

with which to label the probe; and means for detecting the label. The present invention is additionally directed toward a kit for detecting TADG-16 protein, comprising an antibody which is specific for TADG-16 protein or a fragment thereof. The kit may further comprise
5 means to detect the antibody.

The present invention is directed toward a antibody which is specific for TADG-16 protein or a fragment thereof.

The present invention is directed toward a method of screening for compounds that inhibit TADG-16, comprising the steps
10 of: (a) contacting a sample containing TADG-16 protein with a compound; and (b) assaying for TADG-16 protease activity. Typically, a decrease in the TADG-16 protease activity in the presence of the compound relative to TADG-16 protease activity in the absence of the compound is indicative of a compound that inhibits TADG-16.

15 The present invention is directed toward a method of inhibiting expression of TADG-16 in a cell, comprising the step of: (a) introducing a vector expressing TADG-16 antisense mRNA into a cell which hybridizes to endogenous TADG-16 mRNA, thereby inhibiting expression of TADG-16 in the cell. Generally, the inhibition of TADG-
20 16 expression is for treating cancer.

The present invention is directed toward a method of inhibiting a TADG-16 protein in a cell, comprising the step of (a) introducing an antibody specific for a TADG-16 protein or a fragment

thereof into a cell which inhibits the TADG-16 protein. Generally, the inhibition of the TADG-16 protein is for treating cancer.

The present invention is directed toward a method of targeted therapy to an individual, comprising the step of (a) administering a compound having a targeting moiety and a therapeutic moiety to an individual, wherein the targeting moiety is specific for TADG-16. Representative targeting moiety are an antibody specific for TADG-16, a ligand that binds TADG-16 or a ligand binding domain of TADG-16, *e.g.*, a CUB domain, an LDLR domain, etc. Likewise, a representative therapeutic moiety is a radioisotope, a toxin, a chemotherapeutic agent, an immune stimulant or a cytotoxic agent. Typically, the above-described method is useful when the individual suffers from ovarian cancer, breast cancer, lung cancer, prostate cancer, colon cancer or other cancers in which TADG-16 is overexpressed.

The present invention is directed toward a method of diagnosing cancer in an individual, comprising the steps of (a) obtaining a biological sample from an individual; and (b) detecting TADG-16 in the sample. Generally, the presence of TADG-16 in the sample is indicative of the presence of carcinoma in the individual, and the absence of TADG-16 in the sample is indicative of the absence of carcinoma in the individual. Typically, the biological sample is blood, urine, saliva tears, interstitial fluid, ascites fluid, tumor tissue

biopsy or circulating tumor cells. Representative means of detecting TADG-16 are by Northern blot, Western blot, PCR, dot blot, ELISA sandwich assay, radioimmunoassay, DNA array chips or flow cytometry (after labeling tumor cells). This method may be useful in
5 diagnosing cancers such as ovarian, breast, lung, colon, prostate and others with increased TADG-16 expression.

The present invention is also directed to an antisense oligonucleotide having the nucleotide sequence complementary to a TADG-16 mRNA sequence. The present invention is also directed to a
10 composition comprising such an antisense oligonucleotide and a physiologically acceptable carrier therefore.

The present invention is also directed to a method of treating a neoplastic state in an individual in need of such treatment, comprising the step of administering to said individual an effective
15 dose of an antisense oligonucleotide. Preferably, the neoplastic state is ovarian cancer, breast cancer and other cancers that exhibit TADG-16 overexpression. For such therapy, the oligonucleotides alone or in combination with other anti-neoplastic agents can be formulated for a variety of modes of administration, including systemic, topical or
20 localized administration. Techniques and formulations generally can be found in *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA). The oligonucleotide active ingredient is generally combined with a pharmaceutically acceptable carrier such as a

diluent or excipient which can include fillers, extenders, binders, wetting agents, disintegrants, surface active agents or lubricants, depending on the nature of the mode of administration and dosage forms. Typical dosage forms include tablets, powders, liquid
5 preparations including suspensions, emulsions, and solutions, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

For systemic administration, injection is preferred, including intramuscular, intravenous, intraperitoneal and
10 subcutaneous. For injection, the oligonucleotides of the invention are formulated in liquid solutions, preferably in physiologically compatible buffers. In addition, the oligonucleotides can be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms are also included. Dosages that can
15 be used for systemic administration preferably range from about 0.01 mg/kg to 50 mg/kg administered once or twice per day. However, different dosing schedules can be utilized depending on (1) the potency of an individual oligonucleotide at inhibiting the activity of its target DNA, (2) the severity or extent of the pathological disease state,
20 or (3) the pharmacokinetic behavior of a given oligonucleotide.

The present invention is directed toward a method of vaccinating an individual against TADG-16, comprising the steps of (a) inoculating an individual with a TADG-16 protein or fragment thereof

which lacks TADG-16 protease activity. The inoculation with the TADG-16 protein or fragment thereof elicits an immune response in the individual, thereby vaccinating the individual against TADG-16. The vaccination with TADG-16 described herein is intended for an individual who has cancer, is suspected of having cancer or is at risk of getting cancer. The present invention is also directed toward an immunogenic composition, comprising an immunogenic fragment of TADG-16 and an appropriate adjuvant. Generally, the TADG-16 fragment useful for vaccinating an individual consists of a 9-residue fragment up to and including a 20-residue fragment. Preferably, the 9-residue fragments have a sequence such as SEQ ID Nos. 17, 18, 19, 77, 78, 79, 80, 97, 98, 99, 137, 138, 139, 140 or 141. Other TADG-16 fragment useful for vaccinating an individual may be readily determined by an individual having ordinary skill in this art using routine techniques.

The present invention is further directed to a method of regulating the expression of the TADG-16 protein by designing antisense oligonucleotides directed to the DNA encoding the TADG-16 protein. A person having ordinary skill in this art would be able to design such antisense oligonucleotides without undue experimentation.

The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion.

5

EXAMPLE 1

Cloning of the TADG-16 catalytic domain

Using WISH (an amnion derived cell line) cDNA (ATCC) as
10 a template for PCR with degenerate primers designed to the conserved regions surrounding the invariant histidine and serine residues of the catalytic triad of the serine protease family of proteins, a 498 base pair product was obtained that was similar in particular consensus sequences to other known serine proteases (Figure 1).

15 The sequences of the degenerate primers used in the initial PCR are as follows:

Serp-S (Sense): 5'-TGGGTIGTIACIGCIGCICA(CT)TG-3' (SEQ ID No. 8); and

Serp-S (Antisense): 5'-A(AG)IGGICCCICCI(CG)(TA)(AG)TCICC-3'
20 (SEQ ID No. 9).

Reactions were carried out as described by Underwood et al. (*Cancer Res.*, 59, 4435-9 (1999)).

EXAMPLE 2

Detection of TADG-16 mRNA

Using the radioactively labeled catalytic domain as a
5 probe, Northern blot analysis of multiple human tissues revealed that
TADG-16 is highly expressed in normal human testes and in some
ovarian tumors, but not detectable at significant levels in other tissues
examined (Figure 2). More importantly, Northern analysis showed
that the TADG-16 transcript is approximately 1.4 kilobases in length.

10

EXAMPLE 3

Sequence analysis of TADG-16

15 Comparison of the TADG-16 catalytic domain to the EST
database identified a homologous sequence (Accession No.
AA620757) that overlapped a portion of the TADG-16 catalytic
domain clone and also included the 3'-untranslated region and poly
(A) tail of the TADG-16 transcript (Figure 3). Comparison of the
20 catalytic domain clone to the GenBank non-redundant database
identified a genomic cosmid clone (Accession No. AC005361)
homologous to the catalytic domain clone. Using the GRAIL exon
identification program available through the National Center for

Biotechnology Information, potential exons encoding the 5' portion of the TADG-16 transcript were identified.

5

EXAMPLE 4Cloning of the TADG-16 cDNA

A sense PCR primer (T16-F1: 5'-GTCAGGCCGCGGGAGAGGAG-3' (SEQ ID No. 10)) was designed to the
10 cDNA predicted by the Grail program and used in conjunction with an
antisense primer (T16-R2: 5'-ACTCTGGGCCATCAGCTTCT-3' (SEQ ID
No. 11)) designed to the overlapping EST that included the polyA⁺ tail
(GenBank Accession No. AA620757 encoding bases 614 to 1129 of
TADG-16). Additional antisense primers were utilized in 5'-RACE
15 experiments using a human testes cDNA library as template to identify
the 40-most 5' bases. The sequence of the 5'-RACE primers are as
follows:

T16-R6: 5'-CGGAGGGATCACTAAGGTCCTATACGT-3' (SEQ ID No.
12); and

20 T16-R7: 5'-TATACGTTTCAAAGCAGTGCGCCGCCGT-3' (SEQ ID No.
13).

This allowed for the identification of the 1129 bases of the sequence reported herein. Within this 1129 bases, there is a Kozak's consensus

sequence for the initiation of translation, an open reading frame encoding a 314 amino acid protein and a polyadenylation signal.

5

EXAMPLE 5

Tissue-specific expression of TADG-16

Using a previously authenticated semi-quantitative PCR technique (Shigemasa et al., *J. Soc. Gynecological Inv.*, 4, 95-102
10 (1997)), the expression level of the TADG-16 transcript was examined in normal ovarian tissue and ovarian tumor specimens. To do this, a TADG-16-specific PCR product was co-amplified with a PCR product for β -tubulin as an internal control. To amplify a 237 bp PCR product specific for TADG-16, the following primers were used:

15 T16-F2: 5'-GGTCGCCATCATAAACAAC-3' (SEQ ID No. 14); and
T16-R2: 5'-ACTCTGGGCCATCAGCTTCT-3' (SEQ ID No. 15).

The reaction mixture was heated to 94°C for 1.5 min, then 30 cycles of PCR was carried out under the following conditions: 30 sec of denaturation at 94°C, 30 sec of annealing at 62°C and 30 sec of
20 extension at 72°C. A final extension at 72°C was performed for 7 min before the reaction was terminated. These PCR products were electrophoresed through an agarose gel to separate them based on

size. Based on this experiment, TADG-16 appears to be expressed in tumor tissue (Figures 5 & 6).

5

EXAMPLE 6

Expression of TADG-16 in tumors

The expression of the serine protease TADG-16 gene in normal, low malignant potential tumors, and carcinoma (both
10 mucinous and serous type) by quantitative PCR using TADG-16-specific primers was determined (primers directed toward the β -tubulin message were used as an internal standard). These data confirm the overexpression of the TADG-16 surface protease gene in ovarian carcinoma, including both low malignant potential tumors and
15 overt carcinoma. Expression of TADG-16 is increased over normal levels in low malignant potential tumors, and high stage tumors (Stage III) of this group have higher expression of TADG-16 when compared to low stage tumors (Stage 1) (Table 3). In overt carcinoma, serous tumors exhibit the highest levels of TADG-16 expression, while
20 mucinous tumors express levels of TADG-16 comparable with the high stage low malignant potential group.

TABLE 3

Expression of TADG-16						
	Case No.	Code	Stage	Grade	Histology	TADG-16
5	1	1	-	-	-	0.553
	2	1	-	-	-	0.232
	3	1	-	-	-	0.229
	4	1	-	-	-	0.400
	5	1	-	-	-	0.226
10	6	1	-	-	-	0.230
	7	1	-	-	-	0.269
	8	2	-	-	-	0.121
	9	2	-	-	-	0.514
	10	2	-	-	-	0.333
15	11	2	-	-	-	0.323
	12	3				0.732
	13	3				0.487
	14	3				0.850
	15	4	1	1	2	0.815
20	16	4	1	1	3	0.287
	17	4	1	2	2	0.382
	18	4	1	1	1	0.400
	19	4	1	1	2	0.548
	20	4	1	2	4	2.120
25	21	4	1	2	4	1.700
	22	4	1	1	1	1.760
	23	4	1	2	1	1.240
	24	4	2	3	1	1.320
	25	4	2	1	1	0.710
30	26	4	3	1	2	0.828
	27	4	3	1	1	1.730
	28	4	3	1	1	0.510
	29	4	3	1	1	2.320
	30	4	3	1	2	0.792
35	31	4	3	1	3	0.899
	32	4	3	2	1	1.880
	33	4	3	2	1	1.130
	34	4	3	2	3	0.892
	35	4	3	2	3	1.990
40	36	4	3	2	3	0.365
	37	4	3	3	1	1.840
	38	4	3	3	1	1.430
	39	4	3	3	3	0.830
	40	4	3	1	1	1.730
	41	4	3	1	1	2.910

Code: 1, normal ovary; 2, benign tumor (adenoma); 3, LMP tumor; 4, cancer (adenocarcinoma).

Stage = Clinical stage: 1, stage 1; 2, stage 2; 3, stage 3.

Grade = Histological grade: 1, grade 1; 2, grade 2; 3, grade 3.

- 5 Histology: 1, serous carcinoma; 2, mucinous carcinoma; 3, endometrioid carcinoma; 4, clear cell carcinoma.

10

TABLE 4**mRNA Expression Levels of TADG-16 Gene in Ovarian Cancers**

		N	mRNA Expression Levels	
			mean	SD
15	Normal ovary	7	0.306	0.126
	Benign tumor	4	0.323	0.161
	LMP tumor	3	0.690	0.185
	Ovarian cancer	27	1.235	0.692
20	Clinical stage			
	Stage 1	9	1.028	0.695
	Stage 2	2	1.015	0.431
	Stage 3	16	1.380	0.711
25	Histological grade			
	Grade 1	14	1.160	0.794
	Grade 2	9	1.300	0.667
	Grade 3	4	1.355	0.415
30	Histological type			
	Serous	14	1.494	0.688
	Mucinous	5	0.673	0.199
	Endometrioid	6	0.877	0.609
35	Clear Cell	2	1.910	0.297

TABLE 5

5		p-value (unpaired <i>t</i> -test)
10	Tumor type	
	normal vs. benign	0.8473
	normal vs. LMP	0.0046
	normal vs. cancer	0.0014
	benign vs. LMP	0.0375
	benign vs. cancer	0.0148
15	LMP vs. cancer	0.1905
	Stage	
	stage 1 vs. stage 2	0.9808
	stage 1 vs. stage 3	0.2435
	stage 2 vs. stage 3	0.4951
	Grade	
20	grade 1 vs. grade 2	0.6659
	grade 1 vs. grade 3	0.6472
	grade 2 vs. grade 3	0.8830
25	Histology	
	serous vs. mucinous	0.0192
	serous vs. endometrioid	0.0743
	serous vs. clear cell	0.4230
	mucinous vs. endometrioid	0.4937
30	mucinous vs. clear cell	0.0012
	endometrioid vs. clear cell	0.0678

EXAMPLE 7

35

Antisense TADG-16

TADG-16 is cloned and expressed in the opposite orientation such that an antisense RNA molecule (SEQ ID No. 16) is produced. For example, the antisense RNA is used to hybridize to the

complementary RNA in the cell and thereby inhibit translation of TADG-16 RNA into protein.

5

EXAMPLE 8

Peptide ranking

For vaccine or immune stimulation, individual 9-mers to 11-mers of the TADG-16 protein were examined to rank the binding of individual peptides to the top 8 haplotypes in the general population (Parker et al., (1994)). The computer program used for this analyses can be found at <http://www-bimas.dcrf.nih.gov/molbio/hla_bind/>. Table 6 shows the peptide ranking based upon the predicted half-life of each peptide's binding to a particular HLA allele. A larger half-life indicates a stronger association with that peptide and the particular HLA molecule. The TADG-16 peptides that strongly bind to an HLA allele are putative immunogens, and are used to inoculate an individual against hepatitis.

TABLE 6TADG-16 peptide ranking

5	HLA Type & Ranking	Start	Peptide	Predicted Dissociation _{1/2}	SEQ ID No.
	HLA A0201				
	1	70	SLLSHRWAL	592.807	17
10	2	299	LLFFPLLWA	395.296	18
	3	142	KLSAPVTYT	329.937	19
	4	96	WMVQFGQLT	94.077	20
	5	10	ALLLARAGL	79.041	21
	6	252	QIGVVSQGV	71.726	22
15	7	248	GLWYQIGVV	70.769	23
	8	139	ALVKLSAPV	69.552	24
	9	291	SQPDPSWPL	66.602	25
	10	130	YLGNSPYDI	47.991	26
	11	190	TLQEVQVAI	42.774	27
20	12	6	ALLLALLLA	42.278	28
	13	165	FENRTDCWV	34.216	29
	14	71	LLSHRWALT	21.536	30
	15	8	LLALLLARA	19.425	31
	16	297	WPLLFFPLL	17.136	32
25	17	113	QAYYTRYFV	17.002	33
	18	123	NIYLSPRYL	10.339	34
	19	104	TSMPSFWSL	7.352	
	35				
	20	273	NISHHFEWI	7.345	
30	36				
	HLA A0205				
	1	70	SLLSHRWAL	25.200	37
	2	42	IVGGEDAEL	23.800	38
	3	10	ALLLARAGL	21.000	39
35	4	291	SQPDPSWPL	20.160	40
	5	297	WPLLFFPLL	12.600	41
	6	248	GLWYQIGVV	12.000	42
	7	82	HCFETYSDL	6.300	43

	8	142	KLSAPVTTYT	6.000	44
	9	96	WMVQFGQLT	6.000	45
	10	299	LLFFPLLWA	5.100	46
	11	303	PLLWALPLL	4.200	47
5	12	123	NIYLSPRYL	4.200	48
	13	98	VQFGQLTSM	4.080	49
	14	306	WALPLLGPV	3.600	50
	15	71	LLSHRWALT	3.400	51
	16	53	WPWQGSRL	3.150	52
10	17	302	FPLLWALPL	3.150	53
	18	130	YLGNSPYDI	3.000	54
	19	6	ALLLALLLA	3.000	55
	20	190	TLQEVQVAI	3.000	56
HLA A1					
15	1	44	GGEDAELGR	11.250	57
	2	90	LSDPGWMV	7.500	58
	3	143	LSAPVTTYTK	6.000	59
	4	292	QPDPSWPLL	2.500	60
	5	203	MCNHLFLKY	2.500	61
20	6	87	YSDLSDPSG	1.500	62
	7	168	RTDCWVTGW	1.250	63
	8	47	DAELGRWPW	0.900	64
	9	23	SQEAAPLSG	0.675	65
	10	7	LLLALLLAR	0.500	66
25	11	157	CLQASTFEF	0.500	67
	12	202	SMCNHLFLK	0.500	68
	13	111	SLQAYYTRY	0.500	69
	14	125	YLSPRYLGN	0.500	70
	15	152	HIQPICLQA	0.500	71
30	16	79	TAAHCFETY	0.500	72
	17	238	SGGPLACNK	0.500	73
	18	172	WVTGWGYIK	0.400	74
	19	110	WSLQAYYTR	0.300	75
	20	191	LQEVQVAII	0.270	76
HLA A24					
35	1	118	RYFVSNIYL	400.000	77
	2	177	GYIKEDEAL	300.000	78
	3	210	KYSFRKDIF	140.000	79
	4	270	VYTNISHHF	60.000	80
40	5	148	TYTKHIQPI	28.800	81
	6	300	LFFPLLWAL	24.000	82
	7	234	CFGDSGGPL	22.000	83
	8	135	PYDIALVKL	9.600	84

	9	4	RGALLLALL	8.640	85
	10	104	TSMPSEFWSL	8.640	86
	11	296	SWPLLEFFPL	7.500	87
	12	250	WYQIGVVSU	7.200	88
5	13	5	GALLLALLL	7.200	89
	14	95	GWMVQFGQL	7.200	90
	15	199	INNSMCNHL	7.200	91
	16	297	WPLLEFFPLL	7.200	92
	17	291	WQPDPSWPL	7.200	93
10	18	183	EALPSPHTL	7.200	94
	19	86	TYSDLSDPS	7.200	95
	20	10	ALLLARAGL	6.000	96
HLA B7					
	1	297	WPLLEFFPLL	80.000	97
15	2	302	FPLLWALPL	80.000	98
	3	53	WPWQGSRL	80.000	99
	4	292	QPDPSWPLL	24.000	100
	5	145	APVTYTKHI	24.000	101
	6	42	IVGGEDAEL	20.000	102
20	7	10	ALLLARAGL	18.000	103
	8	104	TSMPSEFWSL	12.000	104
	9	183	EALPSPHTL	12.000	105
	10	201	NSMCNHLFL	12.000	106
	11	5	GALLLALLL	12.000	107
25	12	291	SQPDPSWPL	6.000	108
	13	70	SLLSHRWAL	6.000	109
	14	195	QVAIINNSM	5.000	110
	15	116	YTRYFVSNI	4.000	111
	16	199	INNSMCNHL	4.000	112
30	17	82	HCFETYSDL	4.000	113
	18	132	GNSPYDIAL	4.000	114
	19	1	MGARGALLL	4.000	115
	20	63	DSHVCGVSL	4.000	116
HLA B8					
35	1	183	EALPSPHTL	1.600	117
	2	58	SLRLWDSHV	1.200	118
	3	82	HCFETYSDL	1.200	119
	4	116	YTRYFVSNI	1.000	120
	5	2	GARGALLLA	0.800	121
40	6	302	FPLLWALPL	0.800	122
	7	53	WPWQGSRL	0.800	123
	8	31	GPCGRRVIT	0.800	124
	9	297	WPLLEFFPLL	0.800	125

	10	5	GALLLALLL	0.800	126
	11	71	LLSHRWALT	0.400	127
	12	242	LACNKNGLW	0.400	128
	13	10	ALLLARAGL	0.400	129
5	14	70	SLLSHRWAL	0.400	130
	15	63	DSHVCGVSL	0.400	131
	16	89	DLSDPSGWM	0.300	132
	17	132	GNSPYDIAL	0.200	133
	18	140	LVKLSAPVT	0.200	134
10	19	149	YTKHIQPIC	0.200	135
	20	15	RAGLRKPES	0.200	136

HLA B2702

	1	117	GRWPWQVSL	1000.000	137
	2	51	LRSDQEPLY	300.00	138
15	3	263	RRKLPVDRI	200.000	139
	4	74	SRWRVFAGA	100.000	140
	5	128	GRDTSIGRW	100.000	141
	6	266	WRLCGIVSW	60.000	142
	7	3	LRDGAHLC	60.000	143
20	8	34	LRALHSEL	60.000	144
	9	213	FREWIFQAI	20.000	145
	10	18	GRLPHTQRL	20.000	146
	11	101	ERNRVLSRW	20.000	147
	12	227	NRVLSRW RV	20.000	148
25	13	59	SRPKVAALT	20.000	149
	14	40	VRTAGANGT	20.000	150
	15	35	QRLLEVISV	18.000	151
	16	98	CQGD SGPF	10.000	152
	17	112	ARLMVFDKT	6.000	153
30	18	291	WRVFAGAVA	6.000	154
	19	191	GRFLAICQ	6.000	155
	20	157	CLQASTFEF	3.000	156

HLA B4403

	1	122	SNIYLSPRY	30.000	157
35	2	182	DEALPSPHT	24.000	158
	3	45	GEDAELGRW	18.000	159
	4	136	YDIALVKLS	11.250	160
	5	170	DCWVTGWGY	9.000	161
	6	243	ACNKNGLWY	6.000	162
40	7	163	FEFENRTDC	6.000	163
	8	88	SDLSDPSGW	6.000	164
	9	79	TAAHCFETY	6.000	165
	10	278	FEWIKLMA	6.000	166

	11	192	QEVQVAIIN	5.400	167
	12	92	DPSGWMVQF	4.500	168
	13	294	DPSWPLLFF	4.500	169
	14	203	MCNHLFLKY	4.500	170
5	15	76	WALTAAHCF	4.500	171
	16	165	FENRTDCWV	4.000	172
	17	215	KDIFGDMVC	2.500	173
	18	48	AELGRWPWQ	2.400	174
	19	272	TNISHHFEW	2.250	175
10	20	227	AQGGKDACF	2.250	176

Implications

That TADG-16 is found at low levels in some normal
 15 tissues may not detract from its potential usefulness as a tumor
 marker, as there may be an aberrant expression pattern at the
 translational level that, *e.g.*, allows for detection of TADG-16 in tumor
 patients but not in healthy patients, and/or activation of the TADG-16
 enzyme may be necessary for tumor progression. In the case of the
 20 serine protease hepsin, Torres-Rosada et al. demonstrated by down-
 regulating hepsin that hepsin was required for growth of certain
 mammalian cells in culture.

The TADG-16 protein sequence is 314 amino acids in
 length and contains a secretion signal sequence, which suggests that
 25 this protein is functional in an extracellular capacity. A proteolytic
 cleavage site usually associated with protease enzyme activation is
 present downstream from the secretion signal sequence between

amino acid residues 19 and 20. Moreover, the identified clone contains the necessary amino acids characteristic of a functional serine protease catalytic triad, thereby suggesting that this protein may be functioning in a manner that would promote cellular growth
5 or expansion.

Any patents or publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. These patents and publications are herein
10 incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain
15 the ends and advantages mentioned, as well as those inherent therein. The present examples along with the methods, procedures, treatments, molecules, and specific compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention.
20 Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention as defined by the scope of the claims.

WHAT IS CLAIMED IS:

1. DNA encoding a tumor antigen-derived gene (TADG-16) protein, selected from the group consisting of:
 - 5 (a) isolated DNA which encodes a TADG-16 protein;
 - (b) isolated DNA which hybridizes under high stringency conditions to the isolated DNA of (a) above and which encodes a TADG-16 protein; and
 - 10 (c) isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein.
2. The DNA of claim 1, wherein said DNA has the
15 sequence shown in SEQ ID No. 1.
3. The DNA of claim 1, wherein said TADG-16 protein
has the amino acid sequence shown in SEQ ID No. 2.
20
4. An oligonucleotide having the nucleotide sequence complementary to a sequence of claim 1.

5. A composition comprising the oligonucleotide according to claim 4 and a physiologically acceptable carrier therefore.

5

6. A vector comprising the DNA of claim 1 and regulatory elements necessary for expression of said DNA in a cell.

10

7. The vector of claim 6, wherein said DNA encodes a TADG-16 protein having the amino acid sequence shown in SEQ ID No. 2.

15

8. The vector of claim 6, wherein said DNA is positioned in reverse orientation relative to said regulatory elements such that TADG-16 antisense mRNA is produced.

9. A host cell transfected with the vector of claim 6 said vector expressing a TADG-16 protein.

20

10. The host cell of claim 9, wherein said cell is selected from the group consisting of bacterial cells, mammalian cells, plant cells and insect cells.

5

11. The host cell of claim 10, wherein said bacterial cell is *E. coli*.

10

12. Isolated and purified TADG-16 protein coded for by DNA selected from the group consisting of:

15

- (a) isolated DNA which encodes a TADG-16 protein;
- (b) isolated DNA which hybridizes under high stringency conditions to isolated DNA of (a) above and which encodes a TADG-16 protein; and
- (c) isolated DNA differing from the isolated DNAs of (a) and (b) above in codon sequence due to the degeneracy of the genetic code, and which encodes a TADG-16 protein.

20

13. The TADG-16 protein of claim 12, wherein said protein has the amino acid sequence shown in SEQ ID No. 2.

14. An antibody, wherein said antibody is specific for TADG-16 protein or a fragment thereof.

5 15. A method for detecting TADG-16 mRNA in a sample, comprising the steps of:

 (a) contacting a sample with a probe, wherein said probe is specific for TADG-16; and

 (b) detecting binding of said probe to TADG-16 mRNA in
10 said sample.

 16. The method of claim 15, wherein said sample is a biological sample.

15

 17. The method of claim 16, wherein said biological sample is from an individual.

20

 18. The method of claim 17, wherein said individual is suspected of having cancer.

19. A kit for detecting TADG-16 mRNA, comprising:
an oligonucleotide probe, wherein said probe is specific
for TADG-16.

5

20. The kit of claim 19, further comprising:
a label with which to label said probe; and
means for detecting said label.

10

21. A method of detecting TADG-16 protein in a sample,
comprising the steps of:

(a) contacting a sample with an antibody, wherein said
antibody is specific for TADG-16 or a fragment thereof; and

15 (b) detecting binding of said antibody to TADG-16
protein in said sample.

22. The method of claim 21, wherein said sample is a
20 biological sample.

23. The method of claim 22, wherein said biological sample is from an individual.

5 24. The method of claim 23, wherein said individual is suspected of having cancer.

 25. A kit for detecting TADG-16 protein, comprising:
10 an antibody, wherein said antibody is specific for TADG-16 protein or a fragment thereof.

 26. The kit of claim 25, further comprising:
15 means to detect said antibody.

 27. A method of inhibiting endogenous expression of TADG-16 in a cell, comprising the step of:
20 (a) introducing the vector of claim 8 into a cell, wherein expression of said vector produces TADG-16 antisense mRNA in said cell, wherein said TADG-16 antisense mRNA hybridizes to endogenous

TADG-16 mRNA, thereby inhibiting endogenous expression of TADG-16 in said cell.

5 28. A method of inhibiting a TADG-16 protein in a cell, comprising the step of:

 introducing an antibody into a cell, wherein said antibody is specific for a TADG-16 protein or a fragment thereof, wherein binding of said antibody to said TADG-16 protein inhibits said TADG-16 protein.

10 16 protein.

 29. A method of treating a neoplastic state in an individual in need of such treatment, comprising the step of administering to said individual an effective dose of the oligonucleotide of claim 4.

15 administering to said individual an effective dose of the

 30. The method of claim 29, wherein said neoplastic state is selected from the group consisting of ovarian cancer, breast cancer, lung cancer, colon cancer and prostate cancer.

20 state is selected from the group consisting of ovarian cancer, breast

31. A method of vaccinating an individual against TADG-16, comprising the steps of:

inoculating an individual with a TADG-16 protein or fragment thereof, wherein said TADG-16 protein or fragment thereof
5 lack TADG-16 protease activity, wherein said inoculation with said TADG-16 protein or fragment thereof elicits an immune response in said individual, thereby vaccinating said individual against TADG-16.

10 32. The method of claim 31, wherein said TADG-16 fragment is selected from the group consisting of a 9-residue fragment up to a 20-residue fragment.

15 33. The method of claim 32, wherein said 9-residue fragment is selected from the group consisting of SEQ ID Nos. 17, 18, 19, 77, 78, 79, 80, 97, 98, 99, 137, 138, 139, 140 and 141.

20 34. The method of claim 31, wherein said individual has cancer, is suspected of having cancer or is at risk of getting cancer.

35. An immunogenic composition, comprising an immunogenic fragment of a TADG-16 protein and an adjuvant.

5 36. The immunogenic composition of claim 35, wherein said fragment is selected from the group consisting of a 9-residue fragment up to a 20-residue fragment.

10 37. The immunogenic composition of claim 36, wherein said 9-residue fragment is selected from the group consisting of SEQ ID Nos. 17, 18, 19, 77, 78, 79, 80, 97, 98, 99, 137, 138, 139, 140 and 141.

15 38. A method of diagnosing cancer in an individual, comprising the steps of:

- (a) obtaining a biological sample from an individual;
 - (b) detecting TADG-16 in said sample, wherein the
- 20 presence of TADG-16 in said sample is indicative of the presence of carcinoma in said individual, wherein the absence of TADG-16 in said sample is indicative of the absence of carcinoma in said individual.

39. The method of claim 38, wherein said biological sample is selected from the group consisting of blood, urine, saliva, tears, interstitial

5

40. The method of claim 38, wherein said detection of said TADG-16 is by means selected from the group consisting of Northern blot, Western blot, PCR, dot blot, ELISA sandwich assay,
10 radioimmunoassay, DNA array chips and flow cytometry of tumor cells, wherein said tumor cells are labeled.

41. The method of claim 38, wherein said carcinoma is
15 selected from the group consisting of ovarian, breast, lung, colon, prostate and other in which TADG-16 is overexpressed.

42. A method of screening for compounds that inhibit
20 TADG-16, comprising the steps of:

(a) contacting a sample with a compound, wherein said sample comprises TADG-16 protein; and

(b) assaying for TADG-16 protease activity, wherein a decrease in said TADG-16 protease activity in the presence of said compound relative to TADG-16 protease activity in the absence of said compound is indicative of a compound that inhibits TADG-16.

5

43. A method of targeted therapy to an individual, comprising the step of:

administering a compound to an individual, wherein said
10 compound has a targeting moiety and a therapeutic moiety, wherein said targeting moiety is specific for TADG-16.

44. The method of claim 43, wherein said targeting
15 moiety is selected from the group consisting of an antibody specific for TADG-16 and a ligand that binds TADG-16 or a ligand binding domain thereof.

20 45. The method of claim 43, wherein said therapeutic moiety is selected from the group consisting of a radioisotope, a toxin, a chemotherapeutic agent, an immune stimulant and a cytotoxic agent.

46. The method of claim 43, wherein said individual suffers from a cancer selected from the group consisting of ovarian, lung, prostate, colon and others in which TADG-16 is overexpressed.

	1				50
Prom	-----	-----	-----	-----	-----
Tryl	-----	-----	-----	-----	-----
Scce	-----	-----	-----	-----	-----
Heps	XXXXMAQKEG	GRTVPCCSRP	KVAALTAGTL	LLTAIGAAS	WAIVAVLLRS
Tadgl6	-----	-----	-----	-----	-----
	51				100
Prom	-----	-----	-----	-----	-----
Tryl	-----	-----	-----	-----	-----
Scce	-----	-----	-----	-----	-----
Heps	DQEPLYPVQV	SSADARLMVF	DKTEGTWRL	CSSRSNARVA	GLSCEEMGFL
Tadgl6	-----	-----	-----	-----	-----
	101				150
Prom	-----	-----	-----	-----	---MKKLMVVL
Tryl	-----	-----	-----	-----	---MNPLL.IL
Scce	-----	-----	-----	-----	---MAR SLLPLQILL
Heps	RALTHSELDV	RTAGANGTSG	FFCVDEGRLP	ETQRLLEVIS	VCDPCRGRFL
Tadgl6	-----	-----	-----	---MGARGALL	ALLARAGLR
	151				200
Prom	SLIAAAWA..	.EEQNKLVBH	GPCDKTSHPY	QAALYTSGHL	LGGVLIHPL
Tryl	TFVAAALAAP	FDDDDKIVGG	YNCEENSVPY	QVSL.NSGYH	FCGGSLINEQ
Scce	LSLALETAGE	EAQGDKIIDG	APCARGSHPW	QVALLSGNQL	HCGGVLVNER
Heps	AAICQDCGRR	KLPVDRIVGG	RDTSLGRWPW	QVSLRYDGAH	LCGGSLLSGD
Tadgl6	KPTIRGPCGR	RVITSRIVGG	EDAELGRWPW	QGSRLWDSH	VCGVSLLSHR
	201				250
Prom	WVLTAHCKK	..PNLQV...	.FLGKHNLRO	RESS.QEQSS	VVRAVIHPDY
Tryl	WVVSAGHCYK	..SRIQV...	.RLGEHNIEV	LEGN.EQFIN	AAKIIRHPQY
Scce	WVLTAHCKM	..NEYTV...	.HLGSDTLGD	RRA...QRIK	ASKSFRHPGY
Heps	WVLTAHCFP	..ERNRVLRS	WRVFAGAVAQ	ASPH.GLQLG	VQAVVYHGGY
Tadgl6	WALTAHCFE	TYSDLSDPGS	WMVQFGQLTS	MPSFWSLQAY	YTRYFVSNIY
	251				300
PromDAAS	HDQDIMLLRL	ARPAKLSLI	QPLPLERDCS	A..NTTSCHI
TrylDRKT	LNNDIMLIK	SSRAVINARV	STISLPTAPP	A..TGTKCLI
ScceSTQT	HVNDLMLVKL	NSQARLSSMV	KVRLPSRCE	P..PGTTCTV
Heps	LPFRDPNSEE	NSNDIALVHL	SSPLPLTEYI	QPVCLPAAGQ	ALVDGKICTV
Tadgl6	LSPRYLGNSP	Y..DIALVKL	SAPVTYTKHI	QPICLQASTF	EFEVRTDCWV
	301				350
Prom	LGWGKTAD..	G.DFPDTIQ	AYIHLVSREE	CEHA..YPGQ	ITQNLMLCAGD
Tryl	SGWGNLASSG	A.DYPDELQC	LDAPVLSQAK	CEAS..YPGK	ITSNMFCVGF
Scce	SGWGTTTSPD	V.TFPSDLMC	VDVKLISPQD	CTKV..YKOL	LENSMLCAGI
Heps	TGWGNTQYYG	Q.Q.AGVLQE	ARVPIISNDV	CNGADFYGNQ	IKPKMFCAGY
Tadgl6	TGWGYIKEDE	ALPSPHTLQE	VQVAIINNSM	CNHL.FLKYS	FRKDIF..GD
	351				400
Prom	EKYGKDSCQG	DSGGPLVCGD	HLR.....	.GLVSWGNIP	CGSKEKPGVY
Tryl	LEGGKDSCQG	DSGGPVVCNG	QLQ.....	.GVVSWGD.G	CAQKNKPGVY
Scce	PDSKKNACNG	DSGGPLVCRG	TLQ.....	.GLVSWGTFF	CGQPNDPGVY
Heps	PEGGIDACQG	DSGGPFVCE	SISRTPRWRL	CGIVSWG.T	CALAQKPGVY
Tadgl6MG	DSGGPLACN.	...KNGLWYQ	IGVVS.WG.VG	CGRPNRPGVY
	401				443
Prom	TNVCRTNWI	OKTIQAK---	-----	---	(SEQ ID NO: 3)
Tryl	TKVYNYVKWI	KNTIAANS--	-----	---	(SEQ ID NO: 4)
Scce	TQVCKFTKWI	NDTMKKHR--	-----	---	(SEQ ID NO: 5)
Heps	TKVSDFREWI	FQAIKTHSEA	SGMVTOL---	---	(SEQ ID NO: 6)
Tadgl6	TNISHHFEWI	QKLMAQSGMS	QPDPSWPLLF	FPLLWALPLL	GPV (SEQ ID NO: 7)

Fig. 1

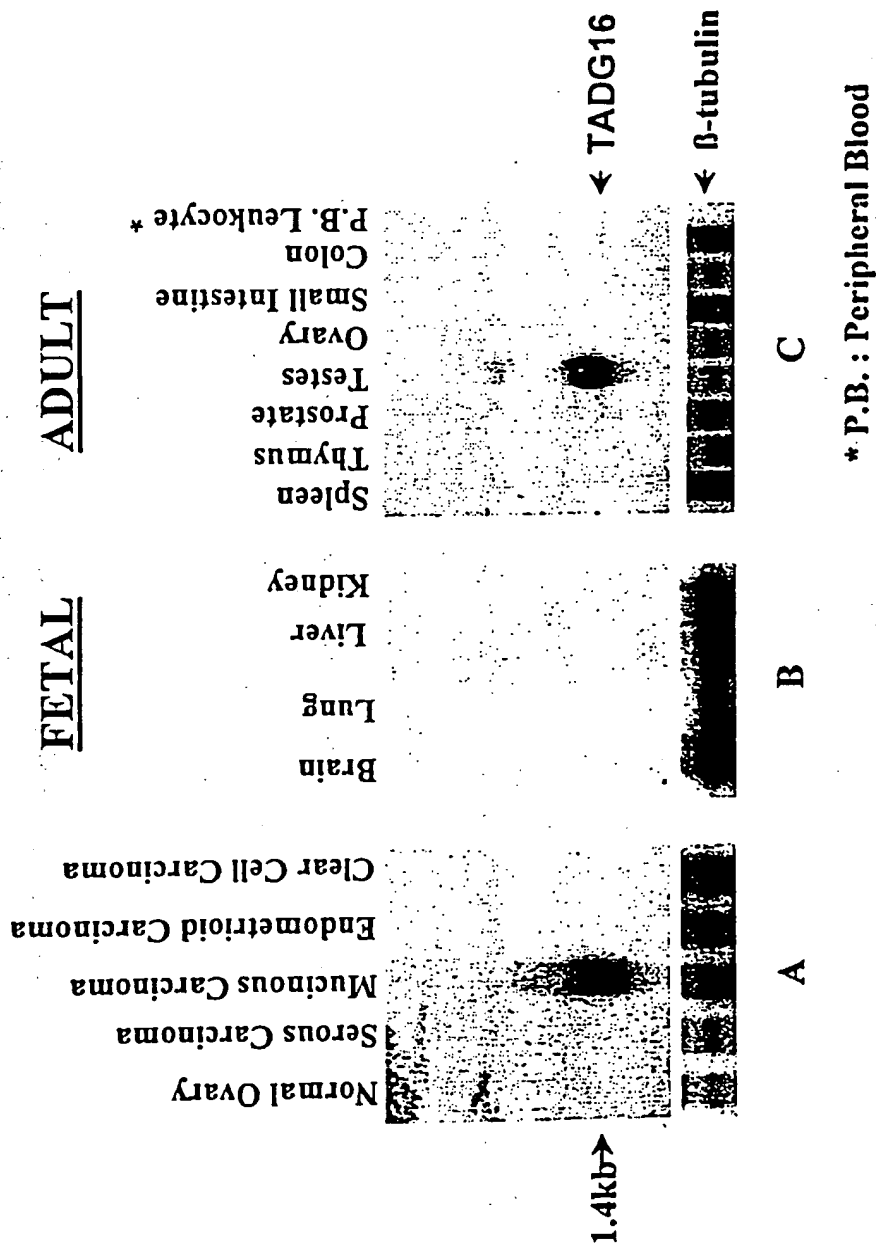


Fig. 2


```

1  TGGGCACTCACGGCGGCGCACTGCTTTGAAACGTATAGTGACCTTAGTGATCCCTCCGGG
   W A L T A A (H) C F E T Y S D L S D P S G -
60  TGGATGGTCCAGTTTGGCCAGCTGACTTCCATGCCATCCTTCTGGAGCCTGCAGGCCTAC
   W M V Q F G Q L T S M P S F W S L Q A Y -
120 TACACCCGTTACTTCGTATCGAATATCTATCTGAGCCCTCGCTACCTGGGGAATTACCC
   Y T R Y F V S N I Y L S P R Y L G N S P -
180 TATGACATTGCCTTGGTGAAGCTGTCTGCACCTGTCACCTACACTAAACACATCCAGCCC
   Y (D) I A L V K L S A P V T Y T K H I Q P -
240 ATCTGTCTCCAGGCCTCCACATTTGAGTTTGAGAACCGGACAGACTGCTGGGTGACTGGC
   I C L Q A S T F E F E N R T D C W V T G -
300 TGGGGGTACATCAAAGAGGATGAGGCACTGCCATCTCCCCACACCCTCCAGGAAGTTCAG
   W G Y I K E D E A L P S P H T L Q E V Q -
360 GTCGCCATCATAAACAACCTCTATGTGCAACCACCTCTTCTCAAGTACAGTTTCCGCAAG
   V A I I N N S M C N H L F L K Y S F R K -
420 GACATCTTTGGAGACATGGTTTGTGCTGGCAATGCCCAAGGCGGGAAGGATGCCTGCTTC
   D I F G D M V C A G N A Q G G K D A C F -
480 GGTGACTCAGGTGGACCC (SEQ ID NO: 177)
   G D (S) G G P (SEQ ID NO: 178)

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Fig. 3A

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1  TTTTTTTTTT TTGAAGAATG CCCTGCAAGG CATCAACTGG AATGTGTTTA
51  TTACCAAACA AGACAGAAGA GAACCAGGGC CTGACTTGGC AGTGGCCCAG
101 GCTGCATGGG CTCAGGTAGG CTCAGACCGG CCCCAGGAGT GGGAGAGCCC
151 AGAGAAGAGG GAAAAAGAGT AGTGGCCAGG AGGGGTCTGG CTGGGACATG
201 CCACTCTGGG CCATCAGCTT CTGGATCCAC TCAAAGTGGT GGCTGATATT
251 GGTGTAGACA CCGGGCCGAT TGGGCGACCA CAGCCCACTC CCCAGCTCAC
301 GACTCCAATC TGATAACCACA GTCCATTCTT GTTACAGGCC AAGGGTCCAC
351 CTGAGTCACC GAAGCAGGCA TCCTTCCCGC ACTTGGGCAT TGCCAGCACA
401 AACCATGTCT CCAAAGATGT CCTTGCGGAA ACTGTACTTG AGGAAGAGGT
451 GGTGTCACAT AGAGTTGTTT ATGATGGCGA ACTGAACTTC CTGGAGGGTG
      (SEQ ID NO: 179)

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Fig. 3B

1 GGGGCGCCCCGGGCGGCGGAGAGGAGGCAGAGGGGGCGTCAGGCCGCGGGAGAGGAG
61 CCCATGGECGCGCGCGGGGCGCTGCTGCTGGCGCTGCTGCTGGCTCGGGCTGGACTCAGG
M G A R G A L L L A L L L A R A G L R

121 AAGCCGGAGTCGCAGGAGGCGGCGCCGTTATCAGGACCATGCGGCCGACGGGTCATCACG
K P E S Q E A A P L S G P C G R R V I T

181 TCGCGCATCGTGGGTGGAGAGGACGCCGAACCTCGGGCGTTGGCCGTGGCAGGGGAGCCTG
S R I V G G E D A E L G R W P W Q G S L

241 CGCCTGTGGGATTCCACGTATGCGGAGTGAGCCTGCTCAGCCACCGCTGGGCACTCAGC
R L W D S H V C G V S L L S H R W A L T

301 GCGGCGCACTGCTTTGAAACGTATAGTGACCTTAGTGATCCCTCCGGGTGGATGGTCCAG
: A A (H) C F E T Y S D L S D P S G W M V Q

361 TTTGGCCAGCTGACTTCCATGCCATCCTTCTGGAGCCTGCAGGCCTACTACACCCGTTAC
F G Q L T S M P S F W S L Q A Y Y T R Y

421 TTCGTATCGAATATCTATCTGAGCCCTCGCTACCTGGGGAATTCACCTATCAGATTGCC
F V S N I Y L S P R Y L G N S P Y (D) I A

481 TTGGTGAAGCTGTCTGCACCTGTACCTACCTAAACACATCCAGCCCATCTGTCTCCAG
L V K L S A P V T Y T K H I Q P I C L Q

541 GCCTCCACATTTGAGTTTGAGAACCGGACAGACTGCTGGGTGACTGGCTGGGGGTACATC
A S T F E F E N R T D C W V T G W G Y I

601 AAAGAGGATGAGGCACTGCCATCTCCCCACACCCTCCAGGAAGTTCAGGTGCGCCATCATA
K E D E A L P S P H T L Q E V Q V A I I

661 AACAACTCTATGTGCAACCACCTCTTCTCAAGTACAGTTTCCGCAAGGACATCTTTGGA
N N S M C N H L F L K Y S F R K D I F G

721 GACATGGTTTGTGCTGGCAATGCCAAGGCGGGAAGGATGCCTGCTTCGGTGACTCAGGT
D M V C A G N A Q G G K D A C F G D (S) G

781 GGACCCTTGGCCTGTAACAAGAATGGACTGTGGTATCAGATTGGAGTCGTGAGCTGGGGA
G P L A C N K N G L W Y Q I G V V S W G

841 GTGGGCTGTGGTCGGCCCAATCGGCCCGGTGTCTACACCAATATCAGCCACCACTTTGAG
V G C G R P N R P G V Y T N I S H H F E

901 TGGATCCAGAAGCTGATGGCCCAGAGTGGCATGTCCAGCCAGACCCCTCCTGGCCGCTA
W I Q K L M A Q S G M S Q P D P S W P L

961 CTCTTTTCCCTCTTCTCTGGGCTCTCCCACTCCTGGGGCCGGTCTGAGCCTACCTGAGC
L F F P L L W A L P L L G P V * (SEQ ID NO: 2)

1021 CCATGCAGCCTGGGGCCAACTGCCAAGTCAGGCCCTGGTTCTCTTCTGTCTTGTGTTGGTA
1081 ATAAACACATTCCAGTTGATGCCTTGCAGGGCATTCTTCAAAAAAAAAA (SEQ ID NO: 1)

Fig. 4

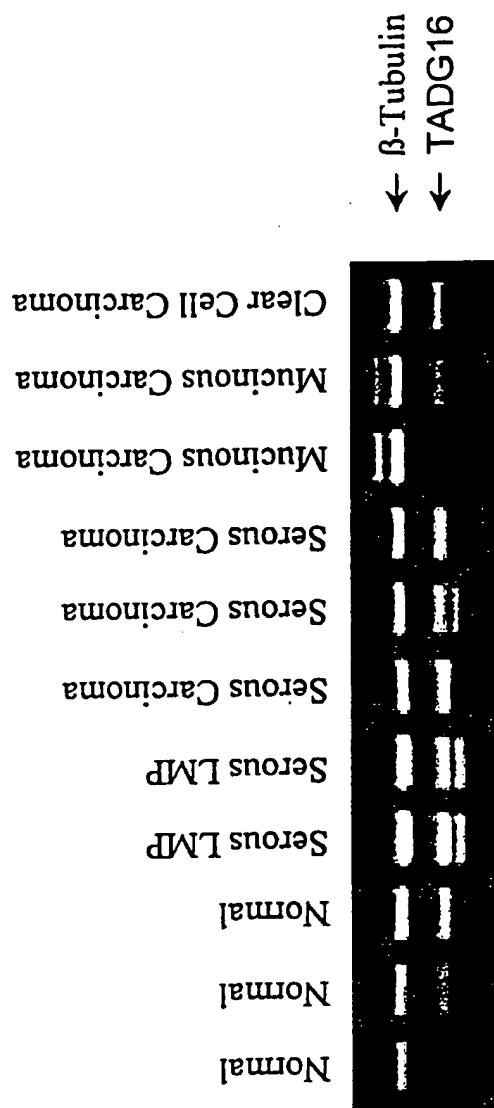


Fig. 5

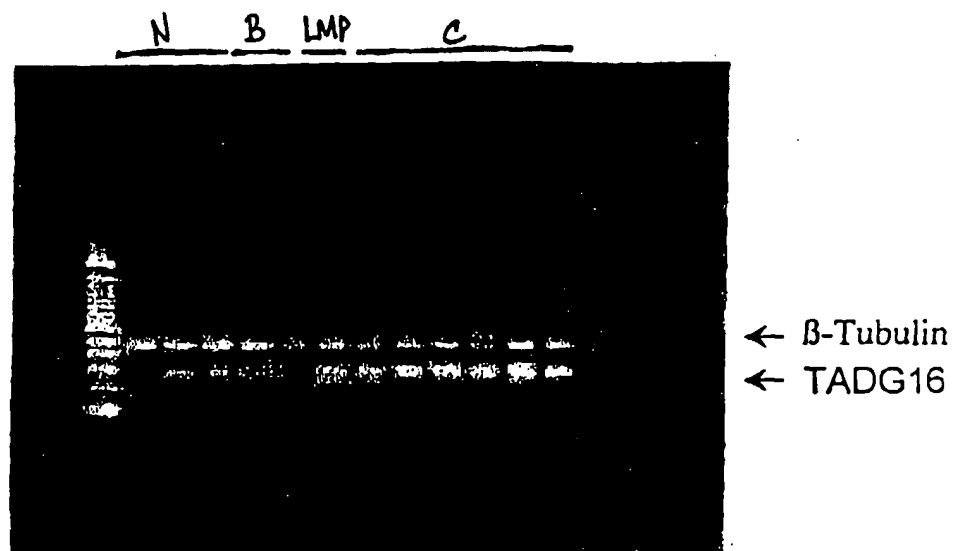


Fig. 6A

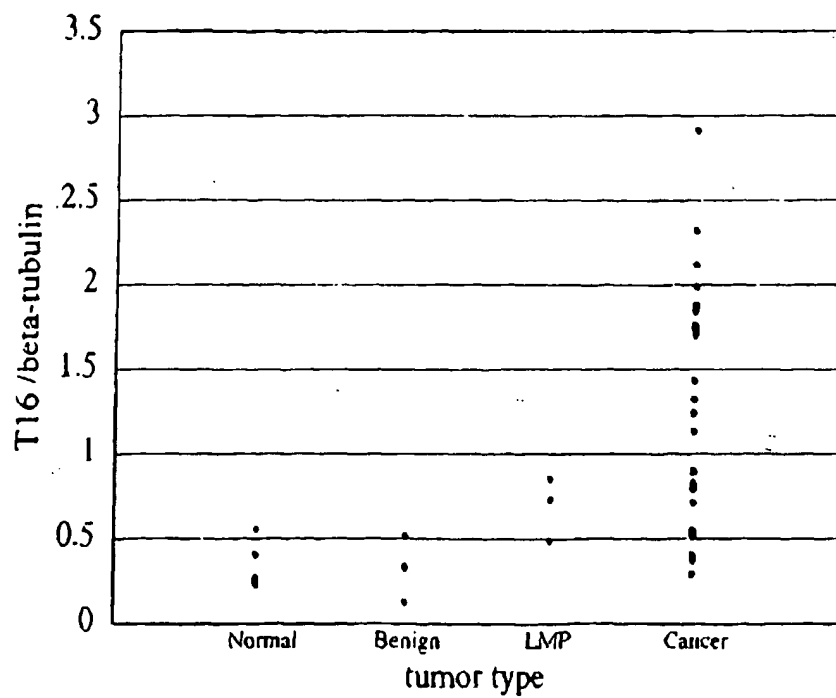


Fig. 6B

SEQUENCE LISTING

<110> O'Brien, Timothy J.
Underwood, Lowell
Shigemasa, Kazushi

<120> Tumor Antigen-Derived Gene 16 (TADG-16): A Novel
Extracellular Serine Protease and Uses Thereof

<130> D6250PCT

<141> 2000-10-13

<150> US 09/418,527

<151> 1999-10-14

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<213> *Homo sapiens*

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<223> TADG-16 cDNA sequence

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tggctcgggc tggactcagg aagccggagt cgcaggaggc ggcgccgtta   150
tcaggaccat gcggccgacg ggtcatcacg tcgcgcatcg tgggtggaga   200
ggacgccgaa ctcgggcggt ggccgtggca ggggagcctg cgctgtggg   250
attcccacgt atgcggagtg agcctgctca gccaccgctg ggcactcacg   300
gcggcgcaact gctttgaaac gtatagtgc cttagtgatc cctccgggtg   350
gatggtccag tttggccagc tgacttccat gccatccttc tggagcctgc   400
aggcctacta caccggttac ttcgatcga atatctatct gagccctcgc   450
tacctgggga attcacccta tgacattgcc ttggtgaagc tgtctgcacc   500
tgtcacctac actaaacaca tccagcccat ctgtctccag gcctccacat   550
ttgagtttga gaaccggaca gactgctggg tgactggctg ggggtacatc   600
aaagaggatg aggactgcc atctccccac accctccagg aagttcagg   650
cgccatcata aacaactcta tgtgcaacca cctcttcctc aagtacagtt   700
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tggatccaga agctgatggc ccagagtggc atgtcccagc cagaccctc   950
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cggctgagc ctacctgagc ccatgcagcc tggggccaac tgccaagtca  1050
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<213> *Homo sapiens*

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Gly	Pro	Cys	Gly	Arg	Arg	Val	Ile	Thr	Ser	Arg	Ile	Val	Gly	Gly	35	40	45
Glu	Asp	Ala	Glu	Leu	Gly	Arg	Trp	Pro	Trp	Gln	Gly	Ser	Leu	Arg	50	55	60
Leu	Trp	Asp	Ser	His	Val	Cys	Gly	Val	Ser	Leu	Leu	Ser	His	Arg	65	70	75
Trp	Ala	Leu	Thr	Ala	Ala	His	Cys	Phe	Glu	Thr	Tyr	Ser	Asp	Leu	80	85	90
Ser	Asp	Pro	Ser	Gly	Trp	Met	Val	Gln	Phe	Gly	Gln	Leu	Thr	Ser	95	100	105
Met	Pro	Ser	Phe	Trp	Ser	Leu	Gln	Ala	Tyr	Tyr	Thr	Arg	Tyr	Phe	110	115	120
Val	Ser	Asn	Ile	Tyr	Leu	Ser	Pro	Arg	Tyr	Leu	Gly	Asn	Ser	Pro	125	130	135
Tyr	Asp	Ile	Ala	Leu	Val	Lys	Leu	Ser	Ala	Pro	Val	Thr	Tyr	Thr	140	145	150
Lys	His	Ile	Gln	Pro	Ile	Cys	Leu	Gln	Ala	Ser	Thr	Phe	Glu	Phe	155	160	165
Glu	Asn	Arg	Thr	Asp	Cys	Trp	Val	Thr	Gly	Trp	Gly	Tyr	Ile	Lys	170	175	180
Glu	Asp	Glu	Ala	Leu	Pro	Ser	Pro	His	Thr	Leu	Gln	Glu	Val	Gln	185	190	195
Val	Ala	Ile	Ile	Asn	Asn	Ser	Met	Cys	Asn	His	Leu	Phe	Leu	Lys	200	205	210
Tyr	Ser	Phe	Arg	Lys	Asp	Ile	Phe	Gly	Asp	Met	Val	Cys	Ala	Gly	215	220	225
Asn	Ala	Gln	Gly	Gly	Lys	Asp	Ala	Cys	Phe	Gly	Asp	Ser	Gly	Gly	230	235	240
Pro	Leu	Ala	Cys	Asn	Lys	Asn	Gly	Leu	Trp	Tyr	Gln	Ile	Gly	Val	245	250	255
Val	Ser	Trp	Gly	Val	Gly	Cys	Gly	Arg	Pro	Asn	Arg	Pro	Gly	Val	260	265	270
Tyr	Thr	Asn	Ile	Ser	His	His	Phe	Glu	Trp	Ile	Gln	Lys	Leu	Met	275	280	285
Ala	Gln	Ser	Gly	Met	Ser	Gln	Pro	Asp	Pro	Ser	Trp	Pro	Leu	Leu	290	295	300
Phe	Phe	Pro	Leu	Leu	Trp	Ala	Leu	Pro	Leu	Leu	Gly	Pro	Val		305	310	

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      20      25
Thr Ser His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu
      35      40
Leu Cys Gly Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala
      50      55
Ala His Cys Lys Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His
      65      70
Asn Leu Arg Gln Arg Glu Ser Ser Gln Glu Gln Ser Ser Val Val
      80      85
Arg Ala Val Ile His Pro Asp Tyr Asp Ala Ala Ser His Asp Gln
      95     100
Asp Ile Met Leu Leu Arg Leu Ala Arg Pro Ala Lys Leu Ser Glu
     110     115
Leu Ile Gln Pro Leu Pro Leu Glu Arg Asp Cys Ser Ala Asn Thr
     125     130
Thr Ser Cys His Ile Leu Gly Trp Gly Lys Thr Ala Asp Gly Asp
     140     145
Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile His Leu Val Ser Arg
     155     160
Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile Thr Gln Asn Met
     170     175
Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser Cys Gln Gly
     185     190
Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg Gly Leu
     200     205
Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro Gly
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Glu Glu Asn Ser Val Pro Tyr Gln Val Ser Leu Asn Ser Gly Tyr
      35      40
His Phe Cys Gly Gly Ser Leu Ile Asn Glu Gln Trp Val Val Ser
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His	Asn	Ile	Glu	Val	Leu	Glu	Gly	Asn	Glu	Gln	Phe	Ile	Asn	Ala	
				80					85					90	
Ala	Lys	Ile	Ile	Arg	His	Pro	Gln	Tyr	Asp	Arg	Lys	Thr	Leu	Asn	
				95					100					105	
Asn	Asp	Ile	Met	Leu	Ile	Lys	Leu	Ser	Ser	Arg	Ala	Val	Ile	Asn	
				110					115					120	
Ala	Arg	Val	Ser	Thr	Ile	Ser	Leu	Pro	Thr	Ala	Pro	Pro	Ala	Thr	
				125					130					135	
Gly	Thr	Lys	Cys	Leu	Ile	Ser	Gly	Trp	Gly	Asn	Thr	Ala	Ser	Ser	
				140					145					150	
Gly	Ala	Asp	Tyr	Pro	Asp	Glu	Leu	Gln	Cys	Leu	Asp	Ala	Pro	Val	
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Leu	Ser	Gln	Ala	Lys	Cys	Glu	Ala	Ser	Tyr	Pro	Gly	Lys	Ile	Thr	
				170					175					180	
Ser	Asn	Met	Phe	Cys	Val	Gly	Phe	Leu	Glu	Gly	Gly	Lys	Asp	Ser	
				185					190					195	
Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Val	Val	Cys	Asn	Gly	Gln	Leu	
				200					205					210	
Gln	Gly	Val	Val	Ser	Trp	Gly	Asp	Gly	Cys	Ala	Gln	Lys	Asn	Lys	
				215					220					225	
Pro	Gly	Val	Tyr	Thr	Lys	Val	Tyr	Asn	Tyr	Val	Lys	Trp	Ile	Lys	
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<212> PRT

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				20					25					30	
Ile	Asp	Gly	Ala	Pro	Cys	Ala	Arg	Gly	Ser	His	Pro	Trp	Gln	Val	
				35					40					45	
Ala	Leu	Leu	Ser	Gly	Asn	Gln	Leu	His	Cys	Gly	Gly	Val	Leu	Val	
				50					55					60	
Asn	Glu	Arg	Trp	Val	Leu	Thr	Ala	Ala	His	Cys	Lys	Met	Asn	Glu	
				65					70					75	
Tyr	Thr	Val	His	Leu	Gly	Ser	Asp	Thr	Leu	Gly	Asp	Arg	Arg	Ala	
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Gln	Arg	Ile	Lys	Ala	Ser	Lys	Ser	Phe	Arg	His	Pro	Gly	Tyr	Ser	
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Thr	Gln	Thr	His	Val	Asn	Asp	Leu	Met	Leu	Val	Lys	Leu	Asn	Ser	
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Gln	Ala	Arg	Leu	Ser	Ser	Met	Val	Lys	Lys	Val	Arg	Leu	Pro	Ser	
				125					130					135	
Arg	Cys	Glu	Pro	Pro	Gly	Thr	Thr	Cys	Thr	Val	Ser	Gly	Trp	Gly	
				140					145					150	

Thr	Thr	Thr	Ser	Pro	Asp	Val	Thr	Phe	Pro	Ser	Asp	Leu	Met	Cys
				155					160					165
Val	Asp	Val	Lys	Leu	Ile	Ser	Pro	Gln	Asp	Cys	Thr	Lys	Val	Tyr
				170					175					180
Lys	Asp	Leu	Leu	Glu	Asn	Ser	Met	Leu	Cys	Ala	Gly	Ile	Pro	Asp
				185					190					195
Ser	Lys	Lys	Asn	Ala	Cys	Asn	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Val
				200					205					210
Cys	Arg	Gly	Thr	Leu	Gln	Gly	Leu	Val	Ser	Trp	Gly	Thr	Phe	Pro
				215					220					225
Cys	Gly	Gln	Pro	Asn	Asp	Pro	Gly	Val	Tyr	Thr	Gln	Val	Cys	Lys
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<222> 1, 2, 3, 4

<223> Sequence of Hepsin, Xaa = Unknown at 1, 2, 3, 4

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Leu	Leu	Leu	Thr	Ala	Ile	Gly	Ala	Ala	Ser	Trp	Ala	Ile	Val	Ala
				35					40					45
Val	Leu	Leu	Arg	Ser	Asp	Gln	Glu	Pro	Leu	Tyr	Pro	Val	Gln	Val
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Thr	Trp	Arg	Leu	Leu	Cys	Ser	Ser	Arg	Ser	Asn	Ala	Arg	Val	Ala
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Gly	Leu	Ser	Cys	Glu	Glu	Met	Gly	Phe	Leu	Arg	Ala	Leu	Thr	His
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Ser	Glu	Leu	Asp	Val	Arg	Thr	Ala	Gly	Ala	Asn	Gly	Thr	Ser	Gly
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Gln	Val	Ser	Leu	Arg	Tyr	Asp	Gly	Ala	His	Leu	Cys	Gly	Gly	Ser
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Leu	Leu	Ser	Gly	Asp	Trp	Val	Leu	Thr	Ala	Ala	His	Cys	Phe	Pro
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Leu	Pro	Leu	Thr	Glu	Tyr	Ile	Gln	Pro	Val	Cys	Leu	Pro	Ala	Ala	
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Ala	Arg	Val	Pro	Ile	Ile	Ser	Asn	Asp	Val	Cys	Asn	Gly	Ala	Asp	
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Phe	Tyr	Gly	Asn	Gln	Ile	Lys	Pro	Lys	Met	Phe	Cys	Ala	Gly	Tyr	
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Pro	Glu	Gly	Gly	Ile	Asp	Ala	Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	
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Phe	Val	Cys	Glu	Asp	Ser	Ile	Ser	Arg	Thr	Pro	Arg	Trp	Arg	Leu	
				365					370					375	
Cys	Gly	Ile	Val	Ser	Trp	Gly	Thr	Gly	Cys	Ala	Leu	Ala	Gln	Lys	
				380					385					390	
Pro	Gly	Val	Tyr	Thr	Lys	Val	Ser	Asp	Phe	Arg	Glu	Trp	Ile	Phe	
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<211> 294

<212> PRT

<213> *Homo sapiens*

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Val	Ile	Thr	Ser	Arg	Ile	Val	Gly	Gly	Glu	Asp	Ala	Glu	Leu	Gly	
				35					40					45	
Arg	Trp	Pro	Trp	Gln	Gly	Ser	Leu	Arg	Leu	Trp	Asp	Ser	His	Val	
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Cys	Gly	Val	Ser	Leu	Leu	Ser	His	Arg	Trp	Ala	Leu	Thr	Ala	Ala	
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His	Cys	Phe	Glu	Thr	Tyr	Ser	Asp	Leu	Ser	Asp	Pro	Ser	Gly	Trp	
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Met	Val	Gln	Phe	Gly	Gln	Leu	Thr	Ser	Met	Pro	Ser	Phe	Trp	Ser	
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Leu	Gln	Ala	Tyr	Tyr	Thr	Arg	Tyr	Phe	Val	Ser	Asn	Ile	Tyr	Leu	
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Ser	Pro	Arg	Tyr	Leu	Gly	Asn	Ser	Pro	Tyr	Asp	Ile	Ala	Leu	Val	
				125					130					135	

Lys	Leu	Ser	Ala	Pro	Val	Thr	Tyr	Thr	Lys	His	Ile	Gln	Pro	Ile
				140					145					150
Cys	Leu	Gln	Ala	Ser	Thr	Phe	Glu	Phe	Glu	Asn	Arg	Thr	Asp	Cys
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Trp	Val	Thr	Gly	Trp	Gly	Tyr	Ile	Lys	Glu	Asp	Glu	Ala	Leu	Pro
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Ser	Pro	His	Thr	Leu	Gln	Glu	Val	Gln	Val	Ala	Ile	Ile	Asn	Asn
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Ser	Met	Cys	Asn	His	Leu	Phe	Leu	Lys	Tyr	Ser	Phe	Arg	Lys	Asp
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Ile	Phe	Gly	Asp	Met	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Ala	Cys	Asn
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Lys	Asn	Gly	Leu	Trp	Tyr	Gln	Ile	Gly	Val	Val	Ser	Trp	Gly	Val
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Gly	Cys	Gly	Arg	Pro	Asn	Arg	Pro	Gly	Val	Tyr	Thr	Asn	Ile	Ser
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His	His	Phe	Glu	Trp	Ile	Gln	Lys	Leu	Met	Ala	Gln	Ser	Gly	Met
				260					265					270
Ser	Gln	Pro	Asp	Pro	Ser	Trp	Pro	Leu	Leu	Phe	Phe	Pro	Leu	Leu
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 serine proteases, n = inosine at 3, 6, 9, 12, 18

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<400> 14
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<210> 19
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<220>
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<210> 20
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<220>
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<220>
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<400> 22
Gln Ile Gly Val Val Ser Trp Gly Val
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<220>
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<400> 23
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<400> 24
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<220>
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<210> 28
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<220>
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<210> 29
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<220>
<223> Residues 165-173 of the TADG-16 protein

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<210> 30
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<220>
<223> Residues 71-79 of the TADG-16 protein

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<220>
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<210> 32
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<220>
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<210> 33
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<220>
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<223> Residues 123-131 of the TADG-16 protein

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<210> 35
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<220>
<223> Residues 104-112 of the TADG-16 protein

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<210> 36
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<220>
<223> Residues 273-281 of the TADG-16 protein

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<210> 37
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<220>
<223> Residues 70-78 of the TADG-16 protein

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<220>
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<220>
<223> Residues 248-256 of the TADG-16 protein

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<220>
<223> Residues 82-90 of the TADG-16 protein

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<220>
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<220>
<223> Residues 299-307 of the TADG-16 protein

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<220>
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<210> 48
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<220>
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<210> 49
<211> 9
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<220>
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<220>
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<210> 51
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<210> 55
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<210> 56
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<210> 60
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<210> 62
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<220>
<223> Residues 87-95 of the TADG-16 protein

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<210> 63
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<210> 64
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<210> 65
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<210> 66
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<212> PRT
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<210> 69
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<210> 70
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<210> 72
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<210> 80
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<210> 82
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<210> 83
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<210> 84
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<210> 85
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<223> Residues 4-12 of the TADG-16 protein

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<210> 86
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<210> 87
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<210> 88
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<210> 89
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<210> 90
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<212> PRT
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<220>
<223> Residues 199-207 of the TADG-16 protein

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<210> 92
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<220>
<223> Residues 297-305 of the TADG-16 protein

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<210> 93
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<212> PRT
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<220>
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Ser Gln Pro Asp Pro Ser Trp Pro Leu
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<210> 94
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<220>
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<210> 95
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<210> 96
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<210> 97
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<220>
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<210> 98
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<210> 99
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<213> *Homo sapiens*

<220>
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<210> 100
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<210> 101
<211> 9
<212> PRT
<213> *Homo sapiens*

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<223> Residues 145-153 of the TADG-16 protein

<400> 101
Ala Pro Val Thr Tyr Thr Lys His Ile
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<210> 102
<211> 9
<212> PRT
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<220>
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Ile Val Gly Gly Glu Asp Ala Glu Leu
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<210> 103
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<212> PRT
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<220>
<223> Residues 10-18 of the TADG-16 protein

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Ala Leu Leu Leu Ala Arg Ala Gly Leu
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<210> 104
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<212> PRT
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<220>
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<210> 105
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<400> 105
Glu Ala Leu Pro Ser Pro His Thr Leu
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<210> 106
<211> 9
<212> PRT
<213> *Homo sapiens*

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Asn Ser Met Cys Asn His Leu Phe Leu
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<210> 107
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<210> 108
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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Ser Gln Pro Asp Pro Ser Trp Pro Leu
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<210> 109
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<400> 109
Ser Leu Leu Ser His Arg Trp Ala Leu
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<210> 110
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<212> PRT
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<210> 111
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 116-124 of the TADG-16 protein

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Tyr Thr Arg Tyr Phe Val Ser Asn Ile
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<210> 112
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 199-207 of the TADG-16 protein

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<210> 113
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 82-90 of the TADG-16 protein

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<210> 114
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 132-140 of the TADG-16 protein

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Gly Asn Ser Pro Tyr Asp Ile Ala Leu
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<210> 115
<211> 9
<212> PRT
<213> *Homo sapiens*

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Met Gly Ala Arg Gly Ala Leu Leu Leu
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<210> 116
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 63-71 of the TADG-16 protein

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Asp Ser His Val Cys Gly Val Ser Leu
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<210> 117
<211> 9
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<210> 118
<211> 9
<212> PRT
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<220>
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<210> 119
<211> 9
<212> PRT
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<210> 121
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<223> Residues 2-10 of the TADG-16 protein

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<210> 122
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<220>
<223> Residues 302-310 of the TADG-16 protein

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<210> 123
<211> 9
<212> PRT
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<220>
<223> Residues 53-61 of the TADG-16 protein

<400> 123
Trp Pro Trp Gln Gly Ser Leu Arg Leu
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<210> 124
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 31-39 of the TADG-16 protein

<400> 124
Gly Pro Cys Gly Arg Arg Val Ile Thr
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<210> 125
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 297-305 of the TADG-16 protein

<400> 125
Trp Pro Leu Leu Phe Phe Pro Leu Leu
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<210> 126
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 5-13 of the TADG-16 protein

<400> 126
Gly Ala Leu Leu Leu Ala Leu Leu Leu
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<210> 127
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 71-79 of the TADG-16 protein

<400> 127
Leu Leu Ser His Arg Trp Ala Leu Thr
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<210> 128
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 242-250 of the TADG-16 protein

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Leu Ala Cys Asn Lys Asn Gly Leu Trp
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<210> 129
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 10-18 of the TADG-16 protein

<400> 129
Ala Leu Leu Leu Ala Arg Ala Gly Leu
5

<210> 130
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 70-78 of the TADG-16 protein

<400> 130
Ser Leu Leu Ser His Arg Trp Ala Leu
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<210> 131
<211> 9
<212> PRT
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<220>
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<210> 132
<211> 9
<212> PRT
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<220>
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<400> 132
Asp Leu Ser Asp Pro Ser Gly Trp Met
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<210> 133
<211> 9
<212> PRT
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<400> 133
Gly Asn Ser Pro Tyr Asp Ile Ala Leu
5

<210> 134
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 140-148 of the TADG-16 protein

<400> 134
Leu Val Lys Leu Ser Ala Pro Val Thr
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<210> 135
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 149-157 of the TADG-16 protein

<400> 135
Tyr Thr Lys His Ile Gln Pro Ile Cys
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<210> 136
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 15-23 of the TADG-16 protein

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Arg Ala Gly Leu Arg Lys Pro Glu Ser
5

<210> 137
<211> 9
<212> PRT
<213> *Homo sapiens*

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<223> Residues 117-125 of the TADG-16 protein

<400> 137
Thr Arg Tyr Phe Val Ser Asn Ile Tyr
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<210> 138
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 51-59 of the TADG-16 protein

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Gly Arg Trp Pro Trp Gln Gly Ser Leu
5

<210> 139
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 263-271 of the TADG-16 protein

<400> 139
Gly Arg Pro Asn Arg Pro Gly Val Tyr
5

<210> 140
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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<400> 140
His Arg Trp Ala Leu Thr Ala Ala His
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<210> 141
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 128-136 of the TADG-16 protein

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Pro Arg Tyr Leu Gly Asn Ser Pro Tyr
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<210> 142
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
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Asn Arg Pro Gly Val Tyr Thr Asn Ile
5

<210> 143
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 3-11 of the TADG-16 protein

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Ala Arg Gly Ala Leu Leu Ala Leu
5

<210> 144
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 34-42 of the TADG-16 protein

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Gly Arg Arg Val Ile Thr Ser Arg Ile
5

<210> 145
<211> 9
<212> PRT
<213> *Homo sapiens*

<220>
<223> Residues 213-221 of the TADG-16 protein

<400> 145
Phe Arg Lys Asp Ile Phe Gly Asp Met
5

<210> 146
<211> 9
<212> PRT
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<210> 147
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<400> 147
Gly Gln Leu Thr Ser Met Pro Ser Phe
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<210> 148
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<220>
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<400> 148
Ala Gln Gly Gly Lys Asp Ala Cys Phe
5

<210> 149
<211> 9
<212> PRT
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<220>
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<400> 149
Leu Arg Leu Trp Asp Ser His Val Cys
5

<210> 150
<211> 9
<212> PRT
<213> *Homo sapiens*

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<223> Residues 40-48 of the TADG-16 protein

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Ser Arg Ile Val Gly Gly Glu Asp Ala
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<210> 151
<211> 9
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<220>
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<400> 151
Arg Arg Val Ile Thr Ser Arg Ile Val
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<210> 152
<211> 9
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<400> 152
Val Gln Phe Gly Gln Leu Thr Ser Met
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<210> 153
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<400> 153
Leu Gln Ala Tyr Tyr Thr Arg Tyr Phe
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<210> 154
<211> 9
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<220>
<223> Residues 291-299 of the TADG-16 protein

<400> 154
Ser Gln Pro Asp Pro Ser Trp Pro Leu
5

<210> 155
<211> 9
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<220>
<223> Residues 191-199 of the TADG-16 protein

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Leu Gln Glu Val Gln Val Ala Ile Ile
5

<210> 156
<211> 9
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<220>
<223> Residues 157-165 of the TADG-16 protein

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Cys Leu Gln Ala Ser Thr Phe Glu Phe
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<210> 157
<211> 9
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<220>
<223> Residues 122-130 of the TADG-16 protein

<400> 157
Ser Asn Ile Tyr Leu Ser Pro Arg Tyr
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<210> 158
<211> 9
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<213> *Homo sapiens*

<220>
<223> Residues 182-190 of the TADG-16 protein

<400> 158
Asp Glu Ala Leu Pro Ser Pro His Thr
5

<210> 159
<211> 9
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<213> *Homo sapiens*

<220>
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<400> 159
Gly Glu Asp Ala Glu Leu Gly Arg Trp
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<210> 160
<211> 9
<212> PRT
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<220>
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<400> 160
Tyr Asp Ile Ala Leu Val Lys Leu Ser
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<210> 161
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Asp Cys Trp Val Thr Gly Trp Gly Tyr
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Ala Cys Asn Lys Asn Gly Leu Trp Tyr
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<210> 163
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Phe Glu Phe Glu Asn Arg Thr Asp Cys
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<210> 164
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Ser Asp Leu Ser Asp Pro Ser Gly Trp
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<210> 165
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<400> 165
Thr Ala Ala His Cys Phe Glu Thr Tyr
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<210> 166
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Phe Glu Trp Ile Gln Lys Leu Met Ala
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<210> 167
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<220>
<223> Residues 192-200 of the TADG-16 protein

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Gln Glu Val Gln Val Ala Ile Ile Asn
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<210> 168
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<223> Residues 92-100 of the TADG-16 protein

<400> 168
Asp Pro Ser Gly Trp Met Val Gln Phe
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<210> 169
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Asp Pro Ser Trp Pro Leu Leu Phe Phe
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<210> 170
<211> 9
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Met Cys Asn His Leu Phe Leu Lys Tyr
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<210> 171
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Trp Ala Leu Thr Ala Ala His Cys Phe
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<210> 172
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<223> Residues 165-173 of the TADG-16 protein

<400> 172
Phe Glu Asn Arg Thr Asp Cys Trp Val
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<210> 173
<211> 9
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<220>
<223> Residues 215-223 of the TADG-16 protein

<400> 173
Lys Asp Ile Phe Gly Asp Met Val Cys
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<210> 174
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<223> Residues 48-56 of the TADG-16 protein

<400> 174
Ala Glu Leu Gly Arg Trp Pro Trp Gln
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<210> 175
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<220>
<223> Residues 272-280 of the TADG-16 protein

<400> 175
Thr Asn Ile Ser His His Phe Glu Trp
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<210> 176
<211> 9
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<213> *Homo sapiens*

<220>
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<400> 176
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<210> 177
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 <212> DNA
 <213> Unknown

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 ctgagccctc gctacctggg gaattcaccc tatgacattg ccttggtgaa 200
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 tgggggtaca tcaaagagga tgaggcactg ccatctcccc acaccctcca 350
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<210> 178
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<220>
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 20 25
 Met Pro Ser Phe Trp Ser Leu Gln Ala Tyr Tyr Thr Arg Tyr Phe
 35 40
 Val Ser Asn Ile Tyr Leu Ser Pro Arg Tyr Leu Gly Asn Ser Pro
 50 55
 Tyr Asp Ile Ala Leu Val Lys Ser Leu Ala Pro Val Thr Tyr Thr
 65 70
 Lys His Ile Gln Pro Ile Cys Leu Gln Ala Ser Thr Phe Glu Phe
 80 85
 Glu Asn Arg Thr Asp Cys Trp Val Thr Gly Trp Gly Tyr Ile Lys
 95 100
 Glu Asp Glu Ala Leu Pro Ser Pro His Thr Leu Gln Glu Val Gln
 110 115
 Val Ala Ile Ile Asn Asn Ser Met Cys Asn His Leu Phe Leu Lys
 125 130
 Tyr Ser Phe Arg Lys Asp Ile Phe Gly Asp Met Val Cys Ala Gly
 140 145
 Asn Ala Gln Gly Gly Lys Asp Ala Cys Phe Gly Asp Ser Gly Gly
 155 160
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<210> 179
 <211> 500
 <212> DNA

<213> Unknown

<220>

<223> Accession No. AA620757

<400> 179

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agagaagagg	gaaaaagagt	agtggccagg	aggggtctgg	ctgggacatg	200
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/28558

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/00, 5/00; C12P 21/06; C07H 21/02

US CL : 435/ 320.1, 325, 69.1; 536/ 23.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/ 320.1, 325, 69.1; 536/ 23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOOPER et al., GENBANK (Accession No. AF058300), National Library of Medicine, Bethesda MD., July 1, 1999 (01.04.1999)	1-4, 9-10
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Y		6-7,11
X	INOUE, M. et al., Cloning and tissue distribution of a novel serine protease esp-1 from human eosinophils. Biochem. Biophys. Res. Commun. November 1998, Vol. 252, No. 2, pages 307-312.	1-4, 6-10
---		-----
Y		11
X	INOUE, M. et al., GENBANK (Accession No. AB031329), National Library of Medicine, Bethesda MD., November 1998, (DNA encoding protein)	1-4, 6-10
---		-----
Y		11
X	ONO PHARM CO LTD., GENBANK (Accession No. X15336), National Library of Medicine, Bethesda MD., May 4, 1999 (04.05.1999)	1-3
---		-----
Y		4-7, 9-11
X	WO 98/36054 a1 (AMRAD OPERATIONS PTY. LTD.) 20 August 1998 (20.08.1998), see Fig.6, see also pages 14, 33, 38, and 40)	1, 3-7, 9-11

<input type="checkbox"/> Further documents are listed in the continuation of Box C.	<input type="checkbox"/> See patent family annex.
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>

Date of the actual completion of the international search

08 January 2001 (08.01.2001)

Date of mailing of the international search report

25 JAN 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
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Washington, D.C. 20231

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/28558

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-11

Remark on Protest

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☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/28558

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1-11, drawn to DNA encoding a TADG-16 protein.

Group 2, claim(s) 12-13, drawn to isolated and purified TADG-16 protein.

Group 3, claim(s) 14, drawn to an antibody.

Group 4, claim(s) 15-20, drawn to a method for detecting TADG-16 mRNA.

Group 5, claim(s) 21-26, drawn to a method for detecting TADG-16 protein.

Group 6, claim(s) 27-28, drawn to a method of inhibiting endogenous expression of TADG-16 in a cell.

Group 7, claim(s) 29-30, drawn to a method of treating a neoplastic state in an individual.

Group 8, claim(s) 31-37, drawn to a method of vaccinating an individual with a TADG-16 fragment or an immunogenic composition consisting of SEQ ID NOs: 17-19, 77-80, 97-99.

Group 9, claim(s) 31-37, drawn to a method of vaccinating an individual with a TADG-16 fragment or an immunogenic composition consisting of SEQ ID NOs: 137-140.

Group 10, claim(s) 31-37, drawn to a method of vaccinating an individual with a TADG-16 fragment or an immunogenic composition consisting of SEQ ID NO: 141.

Group 11, claim(s) 38-41, drawn to a method of diagnosing cancer in an individual.

Group 12, claim(s) 42, drawn to a method of screening for compounds that inhibit TADG-16.

Group 13, claim(s) 43-46, drawn to a method of targeted therapy to an individual.

The inventions listed as Groups 1-11 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Antalis et al. (WO/9836054, August 1998) teach an isolated DNA encoding a tumor antigen which 100% sequence similarity to SEQ ID NO:2 and or a TADG-16 protein (see Fig 6 and attached sequence comparison).